BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033576
Article Type:	Research
Date Submitted by the Author:	12-Aug-2019
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Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, Hepatobiliary tumours < ONCOLOGY, Adult palliative care < PALLIATIVE CARE, Interventional radiology < RADIOLOGY & IMAGING

The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014

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Word count: 3459 words (excluding abstract and references, statements, figures and tables)

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ABSTRACT

Introduction

Relieving obstructive jaundice in inoperable pancreato-biliary cancers improves quality of life and permits chemotherapy. Percutaneous transhepatic cholangiography (PTC) with drainage and/or stenting relieves jaundice but can be associated with significant morbidity and mortality. Percutaneous transhepatic biliary drainage (PTBD) in malignant biliary obstruction was therefore examined in a national cohort to establish risk factors for poor outcomes.

Method

Retrospective study of adult subjects undergoing PTBD for palliation of pancreato-biliary cancer in England between 2001 and 2014, identified from Hospital Episode Statistics (HES). Multivariate logistic regression analysis was used to examine associations with mortality and the need for a repeat PTBD within 2 months.

Results

16,822 subjects analysed (median age 72 (range 19-104) years, 50.3% male). 58% pancreatic and 30% biliary tract cancer. In-hospital and 30-day mortality were 15.3 (95% CI 14.7 - 15.9)% and 23.1 (22.4 - 23.8)% respectively. 20.2% suffered a coded complication within 3 months. Factors associated with 30-day mortality: age (≥81 years odds ratio 2.68 (95% CI 2.37-3.03), p<0.001), increasing comorbidity (Charlson score 20+, 3.10 (2.64-3.65)), p<0.001), pre-existing renal dysfunction (2.37 (2.12-2.65), p<0.001) and non-pancreatic cancer (unspecified biliary tract 1.28 (1.08-1.52), p=0.004). Females had lower mortality (0.91 (0.84-0.98), p=0.011), as did subjects undergoing PTBD in a 'higher volume' provider (84-180 PTBDs per year 0.68 (0.58-0.79), p<0.001).

Conclusion

In subjects undergoing PTBD for the palliation of malignant biliary obstruction, 30-day mortality was high at 23.1%. Mortality was higher in older subjects, males, those with increasing comorbidity, a cancer site other than pancreas and at 'lower-volume' PTBD providers.

Abstract word count: 249

Keywords: Gastrointestinal tumours, hepatobiliary tumours, adult palliative care, interventional radiology

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the largest study to date examining the outcomes of patients undergoing PTBD for unresectable biliary tract obstruction.
- Use of HES database ensures high quality diagnostic, procedural and mortality data at a national level.
- Diagnostic and procedural coding relevant to study locally validated, confirming a high level of accuracy.
- Accuracy of HES database dependent on quality of medical records and the staff coding the records.
- Information relevant to use of PTBD not recorded in HES includes pathology results, use of antibiotics, technical details of PTBD and seniority/experience of radiologist performing procedure.

INTRODUCTION

Jaundice may arise from biliary obstruction by cholangiocarcinoma, pancreatic, duodenal, gallbladder or primary or secondary liver malignancies. The majority of such patients present at a late stage and are unsuitable for curative surgery. Biliary obstruction may impair quality of life and result in pruritus, cholangitis and liver failure, (1,2). In patients who are unsuitable for curative resection, relief of obstructive jaundice improves quality of life, (3,4). Furthermore, biliary drainage can be a bridge to palliative chemotherapy, improving survival in locally advanced and metastatic pancreatic cancer, (5) and in advanced biliary tract cancer, (6,7).

Biliary drainage can be achieved surgically, via endoscopic retrograde cholangiopancreatography (ERCP) or via percutaneous transhepatic cholangiography (PTC). The approach employed will depend on whether the cancer is operable and its location. PTC facilitates external and internal biliary tree drainage and is the primary method of relieving biliary obstruction for malignant lesions above the level of the common hepatic duct, (8) or when ERCP has failed to relieve more distal obstruction. However, percutaneous transhepatic biliary drainage (PTBD) is associated with significant mortality and morbidity, with complications reported to be as high as 30%, including cholangitis, sepsis, haemorrhage and stent blockage, (2).

Case series and randomized controlled trials examining outcomes of PTBD in malignancy have typically involved less than 100 subjects. National data were therefore used to examine unselected outcomes for PTBD in a very large cohort of inoperable pancreato-biliary cancer to establish factors associated with poor outcomes, such as early mortality.

METHODS

Data source

Hospital Episode Statistics (HES) is an administrative database that records all elective and emergency care episodes in English National Health Service hospitals. A unique identifier allows individuals to be followed through their hospital admissions and outpatient attendances. Each recorded episode contains diagnostic, procedural, demographic, administrative and geographical information. Diagnostic data is coded using the International Classification of Diseases version 10 (ICD-10) and procedures coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision (OPCS-4). HES is linked to the Office of National Statistics (ONS) mortality data, providing information on date and cause of death, (9).

Study population

Inclusion criteria

All subjects aged over 18 years undergoing PTBD between 2001 and 2014 with a diagnosis of cancer of the pancreas, gallbladder, liver, intrahepatic bile ducts, small bowel or unspecified bile duct cancer were included. PTBD and diagnosis data was identified by OPCS-4 *(appendix 1)* and ICD-10 *(appendix 2)* coding respectively. All analyses relate to the first PTBD each subject underwent.

Exclusion criteria

Subjects were excluded if they were diagnosed with cancer more than two years prior to their first PTBD or more than 6 months after their first procedure in order to exclude subjects with potentially incorrectly coded diagnoses and to allow for delays in coding of a cancer diagnosis. Subjects who went on to have a surgical resection of their malignancy after PTBD were identified by OPCS-4 coding and were excluded *(appendix 3),* as were those with incomplete demographic data.

Patient and Public involvement

This research was carried out without patient or public involvement.

Validation of PTBD population

To assess the validity of the PTBD population, the number of PTBDs undertaken at University Hospital Birmingham (UHB) between April 2009 and April 2014 that met the study criteria were extracted from the UHB radiology database and compared to the number of PTBDs coded in HES at UHB for the same period.

Study variables and data extraction

Demographics

Demographic data including age, gender and ethnicity were extracted from coding at the time of PTBD. Age was divided into quintiles. Ethnicity was classified into White, Asian or Asian British, Black or Black British, Mixed, any other ethnic group and unknown.

Comorbidity

The Charlson co-morbidity index was calculated using ICD-10 codes for secondary diagnoses, excluding any form of cancer, and divided into five categories by number of comorbidities. The derivation of Charlson score from ICD-10 coding in HES has previously been assessed and found to be valid for assessing comorbidity in patients undergoing surgery for urological cancer. There was an 83% agreement between Charlson scores derived from ICD-10 coding in HES and those derived from ICD-9 comorbidity codes, (10).

Socio-economic status

Deprivation was assessed using the Index of Multiple Deprivations 2007, which is calculated from an aggregate score for each English Lower Layer Super Output Area (LSOA), based on income, employment, health, education, training and skills, barriers to housing and services, crime and living environment, (11). Subjects' LSOAs are recorded in HES based on postcode of residence and deprivation was analysed in quintiles, with 1 being the most and 5 the least deprived.

Healthcare provider

Healthcare providers were stratified by their PTBD volume per year into quintiles.

ERCP

Subjects who had undergone an ERCP prior to their PTBD were identified by OPCS-4 coding *(appendix 4)*.

Outcomes

Outcomes were calculated from the date of the first PTBD and included in-hospital, 7 and 30-day mortality and median survival. Emergency readmissions into any hospital within 30 days of discharge post-PTBD were also identified. The proportion of subjects that suffered complications related to PTBD were identified using ICD-10 coding *(appendix 5)*. Subjects undergoing chemotherapy after their PTBD were identified by ICD-10 (Z080, Z511, Z542, Z926) and OPCS 4 codes (X70, X71, X72, X73, X352, X384).

Ethics

HES includes only pseudonymised data and therefore ethical approval is not necessary. It is available under a data sharing agreement for the purposes of service evaluation.

Statistical analysis

All statistical analyses were carried out using STATA SE v14 (College Station Tx: StataCorp LP). Univariate analysis was performed to identify variables to be included in the final regression models, using χ^2 tests for categorical variables. A multivariate model was produced to examine associations with mortality following adjustment for the variables identified on univariate analyses. A further multivariate model was produced to examine associations with needing a further PTBD procedure, adjusting for the list of variables identified on Univariate analysis. P-values of <0.05 were considered statistically significant. Odds ratios, 95% confidence intervals and p values were generated from the multivariate model. Unadjusted Kaplan Meier analysis was undertaken for 7-day and 30-day mortality, split by age quintile.

RESULTS

Study population

Between 2001 and 2014, 19,525 subjects underwent PTBD for one of the study malignancies. 1,006 subjects were diagnosed with cancer more than two years before or more than 6 months after their PTBD and were excluded. A further 1,438 subjects who underwent potentially curative resection after their PTBD and 259 subjects with incomplete demographic data were also excluded, giving a final study population of 16,822 (*Figure 1)*.

Subject characteristics

The characteristics of the study population and excluded subjects are shown in table 1. 50.3% of subjects were male and the median age was 72 (range 19 to 104) years. 58% of subjects had pancreatic cancer, with malignant neoplasm of the liver and intrahepatic bile ducts accounting for 30.1% of subjects, of whom 90.4% had a diagnosis of cholangiocarcinoma. 86.3% of subjects underwent only one procedure, with a range from one to fifteen and 61.8% had undergone a previous ERCP.

Table 1 Study and excluded subject characteristics

		Included subjects	Excluded subjects	p-value
Sex	**Male**	8465 (50.3%)	527 (52.4%)	0.203
	Female	8357 (49.7%)	479 (47.6%)	
Age	**< 61**	3267 (19.4%)	237 (23.6%)	0.005
	62 to 68	3082 (18.3%)	173 (17.2%)	
	69 to 74	3253 (19.3%)	179 (17.8%)	
	75 to 80	3412 (20.3%)	219 (21.8%)	
	≥81	3808 (22.6%)	198 (19.7%)	
Deprivation	**1**	3258 (19.4%)	183 (18.2%)	0.08
	2	3284 (19.7%)	199 (19.8%)	
	3	3356 (19.5%)	189 (18.8%)	
	4	3453 (20.5%)	201 (20.0%)	
	5	3343 (19.9%)	225 (22.4%)	
	Unknown	71 (0.4%)	9 (0.9%)	
Ethnic Group	**White**	13190 (78.4%)	848 (84.3%)	<0.001
	Asian or Asian British	348 (2.1%)	22 (2.2%)	
	Black or Black British	271 (1.6%)	11 (1.1%)	
	Mixed	32 (0.2%)	*	
	Any other ethnic group	184 (1.1%)	11 (1.1%)	
	Unknown	2797 (16.6%)	111 (11.0%)	
Comorbidities	**< 5**	9456 (56.2%)	660 (65.6%)	<0.001
	5 to 10	1953 (11.6%)	104 (10.3%)	
	10 to 15	3519 (20.9%)	153 (15.2%)	
	15 to 20	1128 (6.7%)	54 (5.4%)	
	> 20	766 (4.6%)	35 (3.5%)	
Type of Cancer	**C17 - Malignant Neoplasm of Small Intestine**	526 (3.1%)	41 (4.1%)	<0.001
	C22 - Malignant Neoplasm of Liver and Intrahepatic Bile Ducts	5069 (30.1%)	332 (33.0%)	
	C23 - Malignant Neoplasm of Gallbladder	715 (4.3%)	45 (4.5%)	
	C24 - Malignant Neoplasm of other and unspecified parts of biliary tract	762 (4.5%)	74 (7.4%)	
	C25 - Malignant Neoplasm of Pancreas	9750 (58%)	514 (51.1%)	
Previous renal failure		1747 (10.4%)	128 (12.7%)	
Previous ERCP		10384 (61.8%)	631 (62.7%)	

Validation

The number of PTBDs meeting the study criteria at UHB between April 2009 and April 2014 was 321 and the number of PTBDs coded in HES for UHB in the same time period was 305 (95%), suggesting misclassification in HES is unlikely. Univariate analysis comparing excluded and included subjects is in table 1. There was no difference in gender between excluded and included subjects. Excluded subjects were younger (under 61 years of age (23.6% vs. 19.4%, p=0.005),) more likely to be white (84.3% vs. 78.4%, p<0.001), have less comorbidities (<5 65.6% vs. 56.2%, p<0.001) and were less likely to have pancreatic cancer (51.1% vs. 58%, p<0.001). Only 259 (1.3%) out of 19,525 subjects were excluded for incomplete demographic data.

Crude mortality and emergency readmission rates

5.2 (95% CI 4.9-5.6)% of subjects died within 7 days of PTBD, 15.3 (95% CI 14.7 – 15.9)% died in hospital and 23.1 (95% CI 22.4 – 23.8)% died within 30 days of their first PTBD. Median survival was 92 (IQR 33 – 242) days and the median length of stay after PTBD was 9 (IQR 4 – 16) days. The emergency readmission rate within 30 days was 20.8 (95% CI 20.1-21.5)%.

Complications

5.9% of subjects suffered a complication within 7 days of their PTBD, and 20% within 3 months (Supplementary table 1). Infection was the most common complication with 2.4% of subjects experiencing this within a week, and 9% within a month (cholangitis 3.9%, sepsis 3.9%, bacterial infection of unspecified site 0.8%, cholecystitis 0.4%). 2.9% of subjects had a code for stent displacement or blockage (mean time to stent blockage or displacement 6.3 (SD 8.6) months) and 2.1% for gastrointestinal haemorrhage. The rate of post-PTBD acute kidney injury was 0.9% within 7 days and 2.4% within 3 months.

Chemotherapy

38.7% of subjects under the age of 61 were coded as undergoing chemotherapy after their PTBD (table 2). This was less common in older subjects: 62 – 68 years (30.4%), 69-74 (23.7%), 75-80 (13.5%) and ≥ 81 (2.5%) (p<0.001). Subjects with pancreatic cancer were the most likely to receive chemotherapy at 22.8%. Over the time period studied, more subjects received chemotherapy after PTBD (2001/2002 13.1%, 2013/2014 27.3% (p<0.001).

Table 2 Rates of pre- and post-percutaneous transhepatic biliary drainage chemotherapy by age, cancer type and year of procedure

Type of Cancer	Number of subjects who had chemotherapy pre-PTBD	Number of subjects who had chemotherapy post-PTBD	P-value
C17 - Malignant Neoplasm of Small Intestine	73 (13.9%)	100 (19%)	<0.001
C22 – Malignant Neoplasm of Liver and Intrahepatic Bile Ducts	251 (5%)	1011 (19.9%)	
C23 – Malignant Neoplasm of Gallbladder	62 (8.7%)	122 (17.1%)	
C24 – Malignant Neoplasm of other and unspecified parts of biliary tract	24 (3.1%)	76 (10%)	
C25 Malignant Neoplasm of Pancreas	855 (8.8%)	2219 (22.8%)	
Age Group			
<61	462 (14.1%)	1263 (38.7%)	<0.001
62-68	352 (11.4%)	937 (30.4%)	
69-74	279 (8.6%)	771 (23.7%)	
75-80	127 (3.7%)	461 (13.5%)	
≥81	45 (1.2%)	96 (2.5%)	
Year of PTBD			
2001/2002	18 (2.0%)	115 (13.1%)	<0.001
2002/2003	48 (4.9%)	137 (13.9%)	
2003/2004	44 (4.8%)	142 (15.4%)	
2004/2005	68 (6.6%)	173 (16.8%)	
2005/2006	53 (4.7%)	206 (18.4%)	
2006/2007	73 (6.0%)	247 (20.5%)	
2007/2008	118 (8.9%)	286 (21.6%)	
2008/2009	98 (7.1%)	305 (22.0%)	
2009/2010	144 (9.2%)	345 (22.0%)	
2010/2011	152 (9.6%)	362 (22.8%)	
2011/2012	145 (8.9%)	384 (23.7%)	
2012/2013	149 (9.4%)	387 (24.5%)	
2013/2014	155 (9.6%)	439 (27.3%)	

Univariate regression analysis

Age, gender, comorbidity, deprivation, pre-existing renal failure, type of cancer, year of procedure and provider PTBD volume were all found to be associated with mortality and adjusted for in the subsequent multivariate analyses (Supplementary tables 2 and 3).

Multivariate regression analysis

Demographic factors and mortality

The results of the multivariate regression analysis for demographic factors associated with mortality are shown in table 3. Age was strongly associated with mortality, with the ≥81 age group having the highest 7-day (2.87 (95% CI 2.23-3.69) p<0.001), in-hospital (3.47 (95% CI 2.97-4.05), p<0.001) and 30-day mortality (2.68 (95% CI 2.37-3.03), p<0.001). The effect of age on 30-day mortality can be seen in figure 2. Females had a better outlook, with lower 7-day (0.82 (95% CI 0.71-0.95), p=0.007) and 30-day mortality (0.91 (95% CI 0.84-0.98), p=0.011).

30-day mortality was associated with deprivation (1.28 (95% CI 1.13-1.44), p<0.001), increased comorbidity (Charlson index 20+, 3.10 (95% CI 2.64-3.65), p<0.001) and pre-existing renal dysfunction (2.37 (95% CI 2.12-2.65), p<0.001), with 7-day mortality following a similar pattern.

Subjects with unspecified bile duct cancer (1.28 (95% CI 1.08-1.52), p=0.004) or liver and intrahepatic bile duct cancer (1.14 (95% CI 1.14-1.24), p=0.004) had a higher 30-day mortality than those with pancreatic cancer. Subjects undergoing ERCP prior to PTBD also had lower 30-day mortality (0.90 (95% CI 0.83-0.97), p=0.007).

Table 3 Multivariate regression analysis of demographic factors associated with mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease

		In-hospital mortality		7-day mortality		30-Day Mortality	
		Odds Ratio	P-value	Odds ratio	P-value	Odds Ratio	P-value
Age Group	< 61	1 (baseline)		1 (baseline group)		1 (baseline)	
	62 to 68	1.49 (1.25-1.77)	<0.001	1.28 (0.96-1.71)	0.095	1.33 (1.16-1.52)	<0.001
	69 to 74	1.66 (1.40-1.96)	<0.001	1.58 (1.20-2.08)	0.001	1.43 (1.25-1.63)	<0.001
	75 to 80	2.36 (2.01-2.77)	<0.001	2.20 (1.70-2.85)	<0.001	1.89 (1.66-2.15)	<0.001
	≥81	3.47 (2.97-4.05)	<0.001	2.87 (2.23-3.69)	<0.001	2.68 (2.37-3.03)	<0.001
Sex	Male	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	Female	0.98 (0.89-1.07)	0.62	0.82 (0.71-0.95)	0.007	0.91 (0.84-0.98)	0.011
Comorbidity Score	< 5	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	5 to 10	1.39 (1.21-1.61)	<0.001	1.46 (1.16-1.82)	0.001	1.38 (1.23-1.56)	<0.001
	10 to 15	1.65 (1.47-1.85)	<0.001	1.72 (1.44-2.06)	<0.001	1.96 (1.78-2.16)	<0.001
	15 to 20	2.15 (1.82-2.54)	<0.001	2.12 (1.65-2.72)	<0.001	2.29 (1.99-2.65)	<0.001
	20+	2.96 (2.48-3.53)	<0.001	2.76 (2.15-3.55)	<0.001	3.10 (2.64-3.65)	<0.001
Deprivation Score	1 (most deprived)	1.49 (1.29-1.72)	<0.001	1.31 (1.05-1.64)	0.017	1.28 (1.13-1.44)	<0.001
	2	1.31 (1.13-1.51)	<0.001	1.12 (0.89-1.41)	0.32	1.21 (1.07-1.37)	0.002
	3	1.08 (0.94-1.36)	0.273	1.09 (0.87-1.36)	0.472	1.01 (0.90-1.29)	0.863
	4	1.18 (1.02-1.36)	0.026	1.06 (0.85-1.33)	0.601	1.14 (1.01-1.29)	0.03
	5 (least deprived)	1 (baseline group)		1 (baseline group)		1 (baseline group)	
Previous renal failure		3.48 (3.09-3.92)	<0.001	2.94 (2.48-3.50)	<0.001	2.37 (2.12-2.65)	<0.001
Type of Cancer	C17 - Malignant Neoplasm of Small Intestine	1.36 (1.07-1.73)	0.013	1.52 (1.07-2.15)	0.019	1.16 (0.94-1.44)	0.161
	C22 - Malignant Neoplasm of Liver and Intrahepatic Bile Ducts	1.26 (1.14-1.39)	<0.001	1.07 (0.91-1.26)	0.403	1.14 (1.04-1.24)	0.004
	C23 - Malignant Neoplasm of Gallbladder	1.30 (1.05-1.61)	0.018	1.09 (0.76-1.56)	0.639	1.18 (0.98-1.42)	0.077
	C24 - Malignant Neoplasm of other and unspecified parts of biliary tract	1.33 (1.09-1.61)	0.005	1.16 (0.86-1.57)	0.336	1.28 (1.08-1.52)	0.004
	C25 - Malignant Neoplasm of Pancreas	1 (baseline group)		1 (baseline group)		1 (baseline group)	
Previous ERCP		0.90 (0.82-0.99)	0.026	0.93 (0.80-1.08)	0.332	0.90 (0.83-0.97)	0.007

Procedural factors and mortality

The results of the multivariate regression analysis of procedural factors associated with mortality are shown in table 4. There was a five-fold variation in 30-day mortality between providers, ranging from 9.1% to 50%. Compared with providers undertaking 1-15 PTBDs per year, there was a significantly decreased in-hospital and 30-day mortality in providers performing 28 – 43 PTBDs per year (0.72 (95% CI 0.62-0.83), p<0.001 and 0.79 (95% CI 0.69-0.89), p<0.001 respectively). In providers performing more than 44 PTBDs per year, there was an even larger decrease in in-hospital (0.68 (95% CI 0.57-0.82), p<0.001), 7-day (0.54 (95% CI 0.40-0.74), p<0.001) and 30-day mortality 0.63 (95% CI 0.54-0.74), p<0.001).

The day of procedure had little influence on mortality with only Sunday having a higher in-hospital (2.54 (95% CI 1.66-3.91), p<0.001) and 30-day mortality (2.20 (95% CI 1.47-3.28), p<0.001) compared to Monday to Thursday. However, the number of subjects who had a PTBD on a Sunday was very small at 114 (0.7%) and therefore these results should be treated with caution. In-hospital mortality post-PTBD on multivariate analysis fell over the period studied, with persistently lower in-hospital mortality between 2013 and 2014 (0.58 (95% CI 0.45-0.74), p<0.001) compared to 2001/2002.

Table 4 Multivariate regression analysis of procedural factors associated with mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease

		In-hospital mortality		7-Day Mortality		30-day mortality	
		Odds Ratio	P-value	Odds Ratio	P-value	Odds Ratio	P-value
PTBD Volume per year	≤15	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	16 to 27	0.79 (0.69-0.90)	0.001	0.92 (0.76-1.13)	0.44	0.93 (0.83-1.04)	0.218
	28 to 43	0.72 (0.62-0.83)	<0.001	0.81 (0.65-1.01)	0.063	0.79 (0.69-0.89)	<0.001
	44 to 83	0.68 (0.57-0.82)	<0.001	0.54 (0.40-0.74)	<0.001	0.63 (0.54-0.74)	<0.001
	84 to 180	0.68 (0.57-0.82)	<0.001	0.71 (0.52-0.95)	0.023	0.68 (0.58-0.79)	<0.001
Pancreaticoduodenectomy Volume	≤1	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	2 to 7	0.96 (0.84-1.11)	0.603	0.91 (0.73-1.12)	0.364	0.90 (0.80-1.01)	0.073
	8 to 23	1.08 (0.94-1.24)	0.278	0.97 (0.79-1.20)	0.79	0.99 (0.88-1.11)	0.814
	24 to 30	1.12 (0.93-1.35)	0.226	0.88 (0.66-1.18)	0.397	0.93 (0.80-1.09)	0.377
	30 to 86	1.01 (0.83-1.22)	0.96	0.87 (0.64-1.18)	0.371	0.95 (0.81-1.12)	0.549
Day of Procedure	Monday to Thursday	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	Friday	1.09 (0.99-1.20)	0.089	0.93 (0.79-1.09)	0.346	0.99 (0.91-1.08)	0.794
	Saturday	1.16 (0.78-1.71)	0.464	1.18 (0.64-2.16)	0.596	1.05 (0.75-1.48)	0.776
	Sunday	2.54 (1.66-3.91)	<0.001	3.69 (2.16-6.30)	<0.001	2.20 (1.47-3.28)	<0.001
	Bank Holiday or Bank Holiday Weekend	1.26 (0.98-1.61)	0.075	0.99 (0.65-1.51)	0.956	0.99 (0.79-1.25)	0.959
Year of PTC	2001/2	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	2002/3	1.11 (0.86-1.44)	0.426	1.15 (0.75-1.76)	0.526	1.05 (0.84-1.31)	0.669
	2003/4	1.11 (0.85-1.45)	0.424	1.45 (0.96-2.19)	0.081	1.05 (0.84-1.31)	0.687
	2004/5	1.07 (0.82-1.38)	0.635	1.02 (0.66-1.58)	0.913	1.03 (0.83-1.29)	0.775
	2005/6	1.14 (0.88-1.47)	0.319	1.24 (0.83-1.87)	0.297	1.08 (0.87-1.34)	0.468
	2006/7	1.03 (0.80-1.33)	0.803	1.04 (0.69-1.58)	0.852	1.03 (0.83-1.27)	0.82
	2007/8	0.90 (0.70-1.16)	0.411	0.88 (0.58-1.33)	0.539	0.78 (0.63-0.97)	0.023
	2008/9	0.93 (0.73-1.19)	0.571	1.20 (0.81-1.78)	0.366	0.96 (0.78-1.19)	0.728
	2009/10	0.84 (0.66-1.08)	0.173	0.99 (0.67-1.47)	0.967	0.84 (0.68-1.03)	0.091
	2010/11	0.70 (0.55-0.90)	0.005	0.71 (0.47-1.07)	0.104	0.78 (0.63-0.96)	0.019
	2011/12	0.73 (0.57-0.94)	0.013	0.89 (0.60-1.33)	0.579	0.86 (0.70-1.05)	0.136
	2012/13	0.71 (0.56-0.91)	0.006	0.80 (0.54-1.19)	0.281	0.92 (0.75-1.13)	0.428
	2013/14	0.58 (0.45-0.74)	<0.001	0.71 (0.48-1.06)	0.094	0.65 (0.53-0.81)	<0.001

Repeat PTBD

The results of the multivariate analyses of factors associated with needing a further PTBD are shown in Table 5. Subjects undergoing an additional PTBD procedure within 2 months of their initial PTBD were younger (81+ years, 0.21 (95% CI 0.16-0.27), p<0.001), less likely to have comorbidities (20+, 0.45 (95% CI 0.29-0.70), p<0.001) and were more likely to have cholangiocarcinoma (2.05 (95% CI 1.77-2.37), p<0.001). Subjects undergoing their procedure in a high-volume centre performing between 84 and 180 procedures per year were much less likely to require a second procedure within 2 months (0.47 (95% CI 0.36-0.62), p<0.001).

Table 5 Multivariate regression analysis of demographic factors associated with the need for a second percutaneous transhepatic biliary drainage for unresectable malignant disease

		Odds Ratio	P-value
Age Group	<61	1 (baseline group)	
	62 to 68	0.81 (0.68 - 0.97)	0.026
	69 to 74	0.67 (0.56 - 0.81)	<0.001
	75 to 80	0.50 (0.41 - 0.61)	<0.001
	81 +	0.21 (0.16 - 0.27)	<0.001
Sex	Male	1 (baseline group)	
	Female	0.84 (0.74 - 0.96)	0.01
Comorbidity Score	< 5	1 (baseline group)	
	5 to 10	0.86 (0.70 - 1.06)	0.161
	10 to 15	0.70 (0.59 - 0.83)	<0.001
	15 to 20	0.30 (0.20 - 0.45)	<0.001
	20+	0.45 (0.29 - 0.70)	<0.001
Spell Year	2001/02	1 (baseline group)	
	2002/03	1.07 (0.69 - 1.67)	0.757
	2003/04	1.00 (0.63 - 1.57)	0.997
	2004/05	0.94 (0.60 - 1.48)	0.803
	2005/06	0.91 (0.58 - 1.42)	0.664
	2006/07	1.32 (0.88 - 1.99)	0.186
	2007/08	1.24 (0.82 - 1.86)	0.308
	2008/09	1.52 (1.03 - 2.26)	0.035
	2009/10	1.78 (1.22 - 2.60)	0.003
	2010/11	1.57 (1.07 - 2.31)	0.022
	2011/12	1.99 (1.37 - 2.90)	<0.001
	2012/13	2.02 (1.39 - 2.94)	<0.001
	2013/14	1.91 (1.31 - 2.79)	0.001
Deprivation score	1 (most deprived)	0.78 (0.63 - 0.97)	0.023
	2	0.97 (0.79 - 1.19)	0.792
	3	0.94 (0.77 - 1.15)	0.543
	4	0.99 (0.81 - 1.21)	0.918
	5 (least deprived)	1 (baseline group)	
PTBD Volume per year	<=15	1 (baseline group)	
	16 to 27	0.72 (0.60 - 0.87)	0.001
	28 to 43	0.40 (0.32 - 0.50)	<0.001
	44 to 83	0.55 (0.42 - 0.72)	<0.001
	84 to 180	0.47 (0.36 - 0.62)	<0.001
Type of Cancer	C17 - Malignant Neoplasm of Small Intestine	1.47 (1.02-2.11)	0.038
	C22 - Malignant Neoplasm of Liver and Intraheptic Bile Ducts	2.05 (1.77-2.37)	<0.001
	C23 - Malignant Neoplasm of Gallbladder	1.68 (1.23-2.31)	0.001
	C24 - Malignant Neoplasm of other and unspecified parts of biliary tract	1.12 (0.77-1.63)	0.55
	C25 - Malignant Neoplasm of Pancreas	1 (baseline group)	

DISCUSSION

This is the largest study to date examining the outcomes of patients undergoing PTBD for unresectable malignant biliary tract obstruction. 7-day and 30-day mortality was 5.2% and 23.1% respectively with a median survival of 92 days. Reported 30-day mortality rates following PTBD vary considerably in the literature. In a 2008 review examining PTBD case series, 30-day mortality for subjects with distal biliary obstruction varied from 2 to 20% and for hilar lesions from 9 to 20%, (2). However, 30-day mortality has been reported to be as high as 39% in other case series, (3, 12-14). In 2012, the results of a large UK audit of biliary drainage and stenting procedures was published. This showed an in-hospital mortality of 19.8% in those with malignant biliary obstruction, (15).

Surgical or endoscopic drainage of the biliary system was not examined in the present study. Surgical drainage is associated with higher postoperative mortality and morbidity and an increased length of stay compared to non-surgical intervention, (16-19). The choice between endoscopic or percutaneous biliary drainage is less clear, as few randomized trials exist, (20). The decision often depends on the level of biliary obstruction. In England, PTBD is often the preferred technique for lesions above the common hepatic duct and when ERCP has failed, (8, 21). Endoscopic drainage, if technically possible, is probably perceived to be safer due to a small, very old, prospective randomized trial from 1987 in hilar and distal bile duct obstruction comparing the two techniques. The endoscopic approach had a higher success rate (81% vs. 61%, p=0.017) and a lower 30-day mortality (15% vs. 33%, p=0.016), (22). However, only plastic stents were used in this study, which does not reflect current practice. There is only one randomized trial comparing PTBD with ERCP in hilar biliary obstruction due to gallbladder cancer, (3). This demonstrated that PTBD had a higher success rate than ERCP (89% vs. 41%, $p < 0.001$) and a lower rate of early cholangitis (11% vs. 48%, $p = 0.02$). In a recent meta-analysis comparing PTBD with ERCP for the relief of malignant jaundice, subjects undergoing PTBD were less likely to develop cholangitis compared to ERCP (0.55 (95% CI 0.36-0.84), p=0.006). However, there was no difference in success rate or 30-day mortality between the two approaches, (23).

The regression analysis in the present study identified subjects with an increased risk of death post PTBD. Older males, with increasing deprivation and comorbidity (especially pre-existing renal dysfunction), and those with a cancer type other than pancreatic had a worse prognosis. A reduced mortality in providers performing a higher volume of PTBDs each year was identified. The authors would therefore recommend that PTBD outcomes are audited and practices from high volume centres with good outcomes adopted.

Biliary obstruction in malignancy may result in pruritus, pain, cholangitis and liver failure, (1, 2). The goal of biliary drainage in inoperable patients is to improve quality of life and, in those with a good performance status, allow palliative chemotherapy. Two studies have shown that biliary drainage can improve quality of life, (3, 4) and it has been shown that gemcitabine-based combinations improve progression free survival in pancreatic cancer (HR 0.91 (95% CI 0.42-1.31), (5). A combination of gemcitabine and cisplatin can improve median survival in advanced biliary tract cancer from 8.1 to 11.7 months (HR 0.64 (95% CI 0.52 - 0.80), p<0.001), (6, 7). However, in our study, it is important to recognise that when considering PTBD, most subjects did not receive chemotherapy after their procedure, with the rates decreasing significantly with age (aged <40 years (40.7% chemotherapy), aged 70 to 80 (17.4%), aged over 80 (2.5%)).

The rate of coded post-procedural complications in our study was high. 5.9% of subjects were coded as experiencing a serious complication within 7 days, and 20.2% within 3 months. However, it was not possible to clarify the relationship between these later complications and the procedure or the underlying malignancy. Complication rates after PTBD vary between case series from 7 to 30%, (2), but cholangitis was common with rates of between 9 and 11% reported, (3, 12-14). The UK audit reported a minor complication rate of 26% and a major complication rate of 7.9%, including a 3.5% rate of sepsis, (15). It has therefore been recommended that all patients undergoing percutaneous drainage receive prophylactic antibiotics prior to their procedure, (24-27). However, there are no national or international guidelines to date on this issue. Rates of cholangitis in these studies were higher in subjects with a low serum albumin or raised CRP, those with proximal or multiple points of intrahepatic biliary obstruction, neoplastic invasion or compression of the duodenum and if Staphylococcus aureus was present at the site of skin puncture. With these factors in mind, patients should be monitored closely post-PTBD for early signs of sepsis, and infection treated aggressively with intravenous antibiotics and fluids. Stent occlusion due to the deposition of a bacterial biofilm and biliary sludge or tumour overgrowth is an important late complication, (28). In the present study, stent blockage or displacement was coded in 6.2% of subjects and rates in other series have been reported at between 5 and 27%, (2, 29, 16). 13.5% of subjects in the current study underwent more than one PTBD procedure. A 2008 review of PTBD series reported recurrence of obstructive jaundice in between 5 and 25% of subjects, with the majority undergoing a repeat PTBD, (2).

Every healthcare provider in England is required to submit diagnostic and procedural data to HES. However, the accuracy of the coding data submitted is a

potential concern as it depends on the quality of the medical records and on the staff coding the records. HES produces a yearly report on the quality of the data received. In the 2012/2013 report, 99.3% of primary diagnoses and 99.9% of primary procedure codes were accurate, (30). In order to validate the accuracy of diagnostic and procedural coding relevant to the present study, the number of PTBDs meeting the study criteria at UHB between 2009 and 2014 was compared to the number submitted to HES. 321 subjects were recorded in HES as undergoing PTBD at UHB and 305 patients were identified from examining local radiology data, giving an accuracy of 95%. HES data is unfortunately not linked to cancer registry data, due to restrictions under which the data is held. Subjects were therefore excluded who had very long periods following an apparent diagnosis of malignancy and PTBD and those with long delays in cancer diagnosis following PTBD. There are some important aspects of the patient's care that are not recorded in HES. Information regarding the exact location of the lesion and whether the procedure was performed with ultrasound guidance, by a supervised trainee, or by an experienced interventional radiologist was not available. Important data such as whether any technical difficulties were encountered, performance status, bilirubin and albumin levels, clotting profile or inflammatory markers were also not available. In particular, prescription data regarding antibiotic use is not recorded, which limits our ability to investigate further the high frequency of septic complications. Recording of chemotherapy in HES may also not be entirely complete, (30).

In conclusion, 30-day mortality in subjects undergoing PTBD for relief of unresectable malignant biliary obstruction was high at 23.1%. Older males and those with increasing comorbidity (especially pre-existing renal dysfunction) and deprivation have a poorer prognosis. Subjects undergoing a PTBD in a provider that performs more than 28 procedures per year have a significantly lower risk of death and there is a large variation in outcomes between providers. In light of the high mortality found in this study, the authors strongly recommend that patients undergo careful multi-disciplinary discussion prior to PTBD in order to identify risk factors for a poor outcome, to treat renal dysfunction and sepsis early, and to confirm that the patient is likely to benefit from PTBD, in terms of either symptom relief or as a bridge to chemotherapy.

Acknowledgements

The authors would like to acknowledge the contribution of Mr. Keith Roberts, consultant hepato-biliary surgeon at University Hospital Birmingham, with identifying relevant surgical procedures.

Author contributions:

James Rees: First author, study concept and design, data interpretation, drafting of manuscript
Jemma Mytton: Acquisition of data, data analysis
Felicity Evison: Acquisition of data, data analysis
Kamarjit Singh Mangat: Study concept and design, critical revision of manuscript for important intellectual content
Prashant Patel: Study concept and design, data interpretation, critical revision of manuscript for important intellectual content
Nigel Trudgill: Senior author, study concept and design, data interpretation, drafting of manuscript, study supervision

Funding:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Conflict of interests:

Kamarjit Singh Mangat is the inventor of a biliary biopsy forceps kit that was first licensed in 2013. The rights have been transferred to Cook Medical and he receives minimal royalties for sales of this device.

Data Availability Statement:

All data relevant to the study are included in the article or uploaded as supplementary information

Figure 1 Study Flowchart

Figure 2 Kaplan Meier unadjusted analysis of 30-day mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease by age

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https://files.digital.nhs.uk/publicationimport/pub11xxx/pub11530/second-annu-data-qual-rep-2013.pdf

Figure 1 Study Flowchart

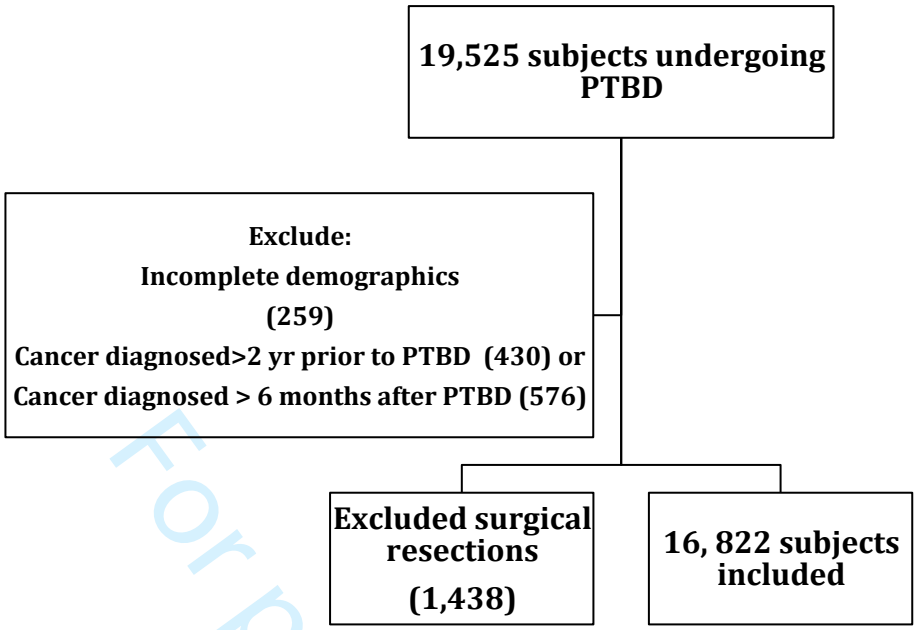
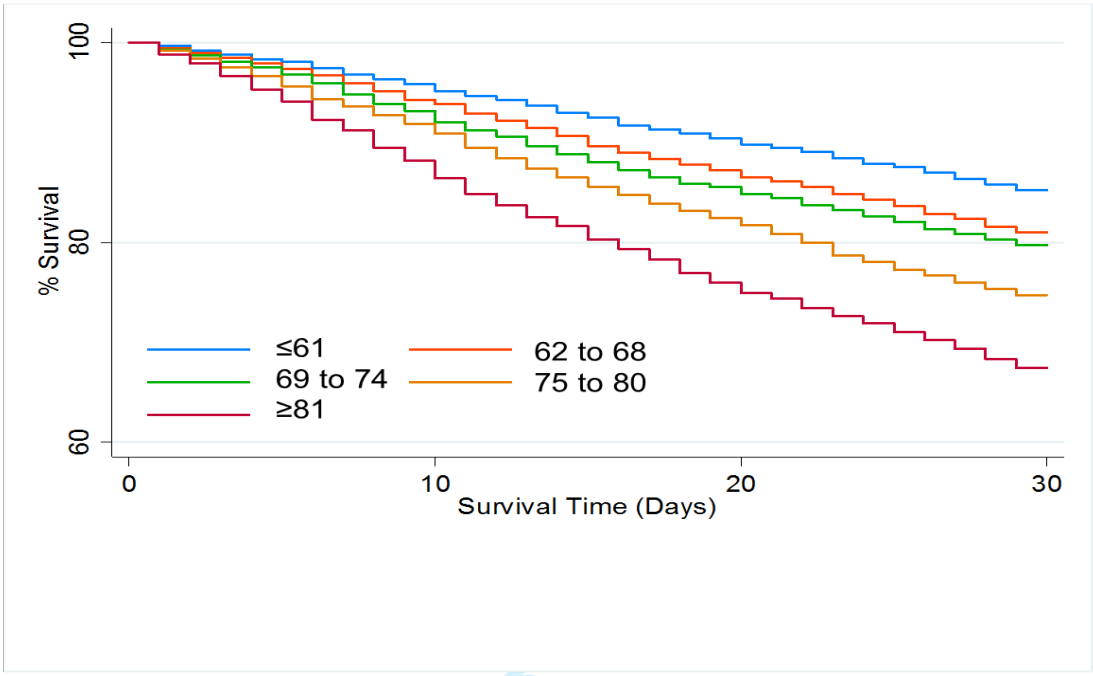


Figure 2 Kaplan Meier unadjusted analysis of 30-day mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease by age



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5, 6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-7
		(*b*) Describe any methods used to examine subgroups and interactions	5-7
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-13
Limitations			13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014; a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033576.R1
Article Type:	Original research
Date Submitted by the Author:	17-Oct-2019
Complete List of Authors:	Rees, James; Dudley Group of Hospitals NHS Trust, Gastroenterology Mytton, Jemma; University Hospitals Birmingham , Evison, Felicity; University Hospitals Birmingham NHS Foundation Trust, Department of Health Informatics Mangat, Kamarjit; National University Hospital, Department of Diagnostic Imaging; University Hospitals Birmingham , Department of Radiology Patel, Prashant; University of Birmingham, Institute of Cancer and Genomic Science Trudgill, Nigel; Sandwell and West Birmingham Hospitals NHS Trust, Department of Gastroenterology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, Hepatobiliary tumours < ONCOLOGY, Adult palliative care < PALLIATIVE CARE, Interventional radiology < RADIOLOGY & IMAGING

The outcomes of biliary drainage by percutaneous transhepatic cholangiography for the palliation of malignant biliary obstruction in England between 2001 and 2014; a retrospective cohort study

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Word count: 3,777 (excluding abstract and references, statements, figures and tables)

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ABSTRACT

Introduction

Relieving obstructive jaundice in inoperable pancreato-biliary cancers improves quality of life and permits chemotherapy. Percutaneous transhepatic cholangiography (PTC) with drainage and/or stenting relieves jaundice but can be associated with significant morbidity and mortality. Percutaneous transhepatic biliary drainage (PTBD) in malignant biliary obstruction was therefore examined in a national cohort to establish risk factors for poor outcomes.

Method

Retrospective study of adult patients undergoing PTBD for palliation of pancreato-biliary cancer in England between 2001 and 2014, identified from Hospital Episode Statistics (HES). Multivariate logistic regression analysis was used to examine associations with mortality and the need for a repeat PTBD within 2 months.

Results

16,822 patients analysed (median age 72 (range 19-104) years, 50.3% male). 58% pancreatic and 30% biliary tract cancer. In-hospital and 30-day mortality were 15.3 (95% CI 14.7 - 15.9)% and 23.1 (22.4 - 23.8)% respectively. 20.2% suffered a coded complication within 3 months. Factors associated with 30-day mortality: age (≥81 years odds ratio 2.68 (95% CI 2.37-3.03), p<0.001), increasing comorbidity (Charlson score 20+, 3.10 (2.64-3.65)), p<0.001), pre-existing renal dysfunction (2.37 (2.12-2.65), p<0.001) and non-pancreatic cancer (unspecified biliary tract 1.28 (1.08-1.52), p=0.004). Females had lower mortality (0.91 (0.84-0.98), p=0.011), as did patients undergoing PTBD in a 'higher volume' provider (84-180 PTBDs per year 0.68 (0.58-0.79), p<0.001).

Conclusion

In patients undergoing PTBD for the palliation of malignant biliary obstruction, 30-day mortality was high at 23.1%. Mortality was higher in older patients, males, those with increasing comorbidity, a cancer site other than pancreas and at 'lower-volume' PTBD providers.

Abstract word count: 249

Keywords: Gastrointestinal tumours, hepatobiliary tumours, adult palliative care, interventional radiology

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the largest study to date examining the outcomes of patients undergoing PTBD for unresectable biliary tract obstruction.
- Use of HES database ensures high quality diagnostic, procedural and mortality data at a national level.
- Diagnostic and procedural coding relevant to study locally validated, confirming a high level of accuracy.
- Accuracy of HES database dependent on quality of medical records and the staff coding the records.
- Information relevant to use of PTBD not recorded in HES includes pathology results, use of antibiotics, technical details of PTBD and seniority/experience of radiologist performing procedure.

INTRODUCTION

Jaundice may arise from biliary obstruction by cholangiocarcinoma, pancreatic, duodenal, gallbladder or primary or secondary liver malignancies. The majority of such patients present at a late stage and are unsuitable for curative surgery. Biliary obstruction may impair quality of life and result in pruritus, cholangitis and liver failure, (1,2). In patients who are unsuitable for curative resection, relief of obstructive jaundice improves quality of life, (3,4). Furthermore, biliary drainage can be a bridge to palliative chemotherapy, improving survival in locally advanced and metastatic pancreatic cancer, (5) and in advanced biliary tract cancer, (6,7).

Biliary drainage can be achieved surgically, via endoscopic retrograde cholangiopancreatography (ERCP) or via percutaneous transhepatic cholangiography (PTC). The approach employed will depend on whether the cancer is operable and its location. PTC facilitates external and internal biliary tree drainage and is the primary method of relieving biliary obstruction for malignant lesions above the level of the common hepatic duct, (8) or when ERCP has failed to relieve more distal obstruction. However, percutaneous transhepatic biliary drainage (PTBD) is associated with significant mortality and morbidity, with complications reported to be as high as 30%, including cholangitis, sepsis, haemorrhage and stent blockage, (2).

Case series and randomized controlled trials examining outcomes of PTBD in malignancy have typically involved less than 100 patients. National data were therefore used to examine unselected outcomes for PTBD in a very large cohort of inoperable pancreato-biliary cancer to establish factors associated with poor outcomes, such as early mortality.

METHODS

Data source

Hospital Episode Statistics (HES) is an administrative database that records all elective and emergency care episodes in English National Health Service hospitals. A unique identifier allows individuals to be followed through their hospital admissions and outpatient attendances. Each recorded episode contains diagnostic, procedural, demographic, administrative and geographical information. Diagnostic data is coded using the International Classification of Diseases version 10 (ICD-10) and procedures coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision (OPCS-4). HES is linked to the Office of National Statistics (ONS) mortality data, providing information on date and cause of death, (9).

Study population

Inclusion criteria

All patients aged over 18 years undergoing PTBD between 2001 and 2014 with a diagnosis of cancer of the pancreas, gallbladder, liver, intrahepatic bile ducts, small bowel or unspecified bile duct cancer were included. PTBD and diagnosis data was identified by OPCS-4 and ICD-10 coding respectively. All analyses relate to the first PTBD each patient underwent.

Exclusion criteria

Patients were excluded if they were diagnosed with cancer more than two years prior to their first PTBD or more than 6 months after their first procedure in order to exclude patients with potentially incorrectly coded diagnoses and to allow for delays in coding of a cancer diagnosis. Patients who went on to have a surgical resection of their malignancy after PTBD were identified by OPCS-4 coding and were excluded, as were those with incomplete demographic data.

Patient and Public involvement

This research was carried out without patient or public involvement.

Validation of PTBD population

To assess the validity of the PTBD population, the number of PTBDs undertaken at University Hospital Birmingham (UHB) between April 2009 and April 2014 that met the study criteria were extracted from the UHB radiology database and compared to the number of PTBDs coded in HES at UHB for the same period.

Study variables and data extraction

Demographics

Demographic data including age, gender and ethnicity were extracted from coding at the time of PTBD. Age was divided into quintiles. Ethnicity was classified into White, Asian or Asian British, Black or Black British, Mixed, any other ethnic group and unknown.

Comorbidity

The Charlson co-morbidity index was calculated using ICD-10 codes for secondary diagnoses, excluding any form of cancer, and divided into five categories by number of comorbidities. The derivation of Charlson score from ICD-10 coding in HES has previously been assessed and found to be valid for assessing comorbidity in patients undergoing surgery for urological cancer. There was an 83% agreement between Charlson scores derived from ICD-10 coding in HES and those derived from ICD-9 comorbidity codes, (10).

Socio-economic status

Deprivation was assessed using the Index of Multiple Deprivations 2007, which is calculated from an aggregate score for each English Lower Layer Super Output Area (LSOA), based on income, employment, health, education, training and skills, barriers to housing and services, crime and living environment, (11). Patients' LSOAs are recorded in HES based on postcode of residence and deprivation was analysed in quintiles, with 1 being the most and 5 the least deprived.

Healthcare provider

Healthcare providers were stratified by their PTBD volume per year into quintiles.

ERCP

Patients who had undergone an ERCP prior to their PTBD were identified by OPCS-4 coding.

Outcomes

Outcomes were calculated from the date of the first PTBD and included in-hospital, 7 and 30-day mortality and median survival. Emergency readmissions into any hospital within 30 days of discharge post-PTBD were also identified. The proportion of patients that suffered complications related to PTBD were identified using ICD-10 coding. Patients undergoing chemotherapy after their PTBD were identified by ICD-10 (Z080, Z511, Z542, Z926) and OPCS 4 codes (X70, X71, X72, X73, X352, X384).

Ethics

HES includes only pseudonymised data and therefore ethical approval is not necessary. It is available under a data sharing agreement for the purposes of service evaluation.

Statistical analysis

All statistical analyses were carried out using STATA SE v14 (College Station Tx: StataCorp LP). Univariate analyses were performed to compare characteristics of included and excluded patients, as well as factors affecting the rates of chemotherapy (Tables 1 and 2 respectively), using χ^2 tests for categorical variables. Bonferroni correction was applied to these analyses and results were considered statistically significant if p-values were <0.0045. A multivariate model was produced to examine associations with mortality following adjustment for the variables identified on univariate analyses. A further multivariate model was produced to examine associations with needing a further PTBD procedure, adjusting for the list of variables identified on Univariate analysis. In the multivariate analyses p-values of <0.05 were considered statistically significant. Odds ratios, 95% confidence intervals and p values were generated from the multivariate model. Unadjusted Kaplan Meier analysis was undertaken for 7-day and 30-day mortality, split by age quintile.

RESULTS

Study population

Between 2001 and 2014, 19,525 patients underwent PTBD for one of the study malignancies. 1,006 patients were diagnosed with cancer more than two years before or more than 6 months after their PTBD and were excluded. A further 1,438 patients who underwent potentially curative resection after their PTBD and 259 patients with incomplete demographic data were also excluded, giving a final study population of 16,822 (*Figure 1)*.

Patient characteristics

The characteristics of the study population and excluded patients are shown in table 1. 50.3% of patients were male and the median age was 72 (range 19 to 104) years. 58% of patients had pancreatic cancer, with malignant neoplasm of the liver and intrahepatic bile ducts accounting for 30.1% of patients, of whom 90.4% had a diagnosis of cholangiocarcinoma. 86.3% of patients underwent only one procedure, with a range from one to fifteen and 61.8% had undergone a previous ERCP. 57.9% of patients undergoing prior ERCP had their PTBD carried out on the same admission, indicating that the PTBD was likely a salvage procedure.

Table 1 Study and excluded patient characteristics

		Included patients	Excluded patients	p-value
Sex	**Male**	8465 (50.3%)	527 (52.4%)	0.203
	Female	8357 (49.7%)	479 (47.6%)	
Age	**< 61**	3267 (19.4%)	237 (23.6%)	0.005
	62 to 68	3082 (18.3%)	173 (17.2%)	
	69 to 74	3253 (19.3%)	179 (17.8%)	
	75 to 80	3412 (20.3%)	219 (21.8%)	
	≥81	3808 (22.6%)	198 (19.7%)	
Deprivation	**1**	3258 (19.4%)	183 (18.2%)	0.08
	2	3284 (19.7%)	199 (19.8%)	
	3	3356 (19.5%)	189 (18.8%)	
	4	3453 (20.5%)	201 (20.0%)	
	5	3343 (19.9%)	225 (22.4%)	
	Unknown	71 (0.4%)	9 (0.9%)	
Ethnic Group	**White**	13190 (78.4%)	848 (84.3%)	<0.001
	Asian or Asian British	348 (2.1%)	22 (2.2%)	
	Black or Black British	271 (1.6%)	11 (1.1%)	
	Mixed	32 (0.2%)	*	
	Any other ethnic group	184 (1.1%)	11 (1.1%)	
	Unknown	2797 (16.6%)	111 (11.0%)	
Comorbidities	**< 5**	9456 (56.2%)	660 (65.6%)	<0.001
	5 to 10	1953 (11.6%)	104 (10.3%)	
	10 to 15	3519 (20.9%)	153 (15.2%)	
	15 to 20	1128 (6.7%)	54 (5.4%)	
	> 20	766 (4.6%)	35 (3.5%)	
Type of Cancer	**C17 - Malignant Neoplasm of Small Intestine**	526 (3.1%)	41 (4.1%)	<0.001
	C22 - Malignant Neoplasm of Liver and Intrahepatic Bile Ducts	5069 (30.1%)	332 (33.0%)	
	C23 - Malignant Neoplasm of Gallbladder	715 (4.3%)	45 (4.5%)	
	C24 - Malignant Neoplasm of other and unspecified parts of biliary tract	762 (4.5%)	74 (7.4%)	
	C25 - Malignant Neoplasm of Pancreas	9750 (58%)	514 (51.1%)	
Previous renal failure		1747 (10.4%)	128 (12.7%)	
Previous ERCP		10384 (61.8%)	631 (62.7%)	

Validation

The number of PTBDs meeting the study criteria at UHB between April 2009 and April 2014 was 321 and the number of PTBDs coded in HES for UHB in the same time period was 305 (95%), suggesting misclassification in HES is unlikely. Univariate analysis comparing excluded and included patients is in table 1. There was no difference in gender between excluded and included patients. Excluded patients were younger (under 61 years of age (23.6% vs. 19.4%, p=0.005),) more likely to be white (84.3% vs. 78.4%, p<0.001), have less comorbidities (<5 65.6% vs. 56.2%, p<0.001) and were less likely to have pancreatic cancer (51.1% vs. 58%, p<0.001). Only 259 (1.3%) out of 19,525 patients were excluded for incomplete demographic data.

Crude mortality and emergency readmission rates

5.2 (95% CI 4.9-5.6)% of patients died within 7 days of PTBD, 15.3 (95% CI 14.7 – 15.9)% died in hospital and 23.1 (95% CI 22.4 – 23.8)% died within 30 days of their first PTBD. Median survival was 92 (IQR 33 – 242) days and the median length of stay after PTBD was 9 (IQR 4 – 16) days. The emergency readmission rate within 30 days was 20.8 (95% CI 20.1-21.5)%.

Complications

5.9% of patients suffered a complication within 7 days of their PTBD, and 20% within 3 months. Infection was the most common complication with 2.4% of patients experiencing this within a week, and 9% within a month (cholangitis 3.9%, sepsis 3.9%, bacterial infection of unspecified site 0.8%, cholecystitis 0.4%). 2.9% of patients had a code for stent displacement or blockage (mean time to stent blockage or displacement 6.3 (SD 8.6) months) and 2.1% for gastrointestinal haemorrhage. The rate of post-PTBD acute kidney injury was 0.9% within 7 days and 2.4% within 3 months.

Chemotherapy

38.7% of patients under the age of 61 were coded as undergoing chemotherapy after their PTBD (table 2). This was less common in older patients: 62 – 68 years (30.4%), 69-74 (23.7%), 75-80 (13.5%) and ≥ 81 (2.5%) (p<0.001). Patients with pancreatic cancer were the most likely to receive chemotherapy at 22.8%. Over the time period studied, more patients received chemotherapy after PTBD (2001/2002 13.1%, 2013/2014 27.3% (p<0.001).

Table 2 Rates of pre- and post-percutaneous transhepatic biliary drainage chemotherapy by age, cancer type and year of procedure

Type of Cancer	Number of patients who had chemotherapy pre-PTBD	Number of patients who had chemotherapy post-PTBD	P-value
C17 - Malignant Neoplasm of Small Intestine	73 (13.9%)	100 (19%)	<0.001
C22 – Malignant Neoplasm of Liver and Intrahepatic Bile Ducts	251 (5%)	1011 (19.9%)	
C23 – Malignant Neoplasm of Gallbladder	62 (8.7%)	122 (17.1%)	
C24 – Malignant Neoplasm of other and unspecified parts of biliary tract	24 (3.1%)	76 (10%)	
C25 Malignant Neoplasm of Pancreas	855 (8.8%)	2219 (22.8%)	
Age Group			
<61	462 (14.1%)	1263 (38.7%)	<0.001
62-68	352 (11.4%)	937 (30.4%)	
69-74	279 (8.6%)	771 (23.7%)	
75-80	127 (3.7%)	461 (13.5%)	
≥81	45 (1.2%)	96 (2.5%)	
Year of PTBD			
2001/2002	18 (2.0%)	115 (13.1%)	<0.001
2002/2003	48 (4.9%)	137 (13.9%)	
2003/2004	44 (4.8%)	142 (15.4%)	
2004/2005	68 (6.6%)	173 (16.8%)	
2005/2006	53 (4.7%)	206 (18.4%)	
2006/2007	73 (6.0%)	247 (20.5%)	
2007/2008	118 (8.9%)	286 (21.6%)	
2008/2009	98 (7.1%)	305 (22.0%)	
2009/2010	144 (9.2%)	345 (22.0%)	
2010/2011	152 (9.6%)	362 (22.8%)	
2011/2012	145 (8.9%)	384 (23.7%)	
2012/2013	149 (9.4%)	387 (24.5%)	
2013/2014	155 (9.6%)	439 (27.3%)	

Univariate regression analysis

Age, gender, comorbidity, deprivation, pre-existing renal failure, type of cancer, year of procedure and provider PTBD volume were all found to be associated with mortality and adjusted for in the subsequent multivariate analyses.

Multivariate regression analysis

Demographic factors and mortality

The results of the multivariate regression analysis for demographic factors associated with mortality are shown in table 3. Age was strongly associated with mortality, with the ≥81 age group having the highest 7-day (2.87 (95% CI 2.23-3.69) p<0.001), in-hospital (3.47 (95% CI 2.97-4.05), p<0.001) and 30-day mortality (2.68 (95% CI 2.37-3.03), p<0.001). Females had a better outlook, with lower 7-day (0.82 (95% CI 0.71-0.95), p=0.007) and 30-day mortality (0.91 (95% CI 0.84-0.98), p=0.011).

30-day mortality was associated with deprivation (1.28 (95% CI 1.13-1.44), p<0.001), increased comorbidity (Charlson index 20+, 3.10 (95% CI 2.64-3.65), p<0.001) and pre-existing renal dysfunction (2.37 (95% CI 2.12-2.65), p<0.001), with 7-day mortality following a similar pattern.

Patients with unspecified bile duct cancer (1.28 (95% CI 1.08-1.52), p=0.004) or liver and intrahepatic bile duct cancer (1.14 (95% CI 1.14-1.24), p=0.004) had a higher 30-day mortality than those with pancreatic cancer. Patients undergoing ERCP prior to PTBD also had lower 30-day mortality (0.90 (95% CI 0.83-0.97), p=0.007).

Table 3 Multivariate regression analysis of demographic and clinical factors associated with mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease

		In-hospital mortality		7-day mortality		30-Day Mortality	
		Odds Ratio	P-value	Odds ratio	P-value	Odds Ratio	P-value
Age Group	< 61	1 (baseline)		1 (baseline group)		1 (baseline)	
	62 to 68	1.49 (1.25-1.77)	<0.001	1.28 (0.96-1.71)	0.095	1.33 (1.16-1.52)	<0.001
	69 to 74	1.66 (1.40-1.96)	<0.001	1.58 (1.20-2.08)	0.001	1.43 (1.25-1.63)	<0.001
	75 to 80	2.36 (2.01-2.77)	<0.001	2.20 (1.70-2.85)	<0.001	1.89 (1.66-2.15)	<0.001
	≥81	3.47 (2.97-4.05)	<0.001	2.87 (2.23-3.69)	<0.001	2.68 (2.37-3.03)	<0.001
Sex	Male	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	Female	0.98 (0.89-1.07)	0.62	0.82 (0.71-0.95)	0.007	0.91 (0.84-0.98)	0.011
Comorbidity Score	< 5	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	5 to 10	1.39 (1.21-1.61)	<0.001	1.46 (1.16-1.82)	0.001	1.38 (1.23-1.56)	<0.001
	10 to 15	1.65 (1.47-1.85)	<0.001	1.72 (1.44-2.06)	<0.001	1.96 (1.78-2.16)	<0.001
	15 to 20	2.15 (1.82-2.54)	<0.001	2.12 (1.65-2.72)	<0.001	2.29 (1.99-2.65)	<0.001
	20+	2.96 (2.48-3.53)	<0.001	2.76 (2.15-3.55)	<0.001	3.10 (2.64-3.65)	<0.001
Deprivation Score	1 (most deprived)	1.49 (1.29-1.72)	<0.001	1.31 (1.05-1.64)	0.017	1.28 (1.13-1.44)	<0.001
	2	1.31 (1.13-1.51)	<0.001	1.12 (0.89-1.41)	0.32	1.21 (1.07-1.37)	0.002
	3	1.08 (0.94-1.36)	0.273	1.09 (0.87-1.36)	0.472	1.01 (0.90-1.29)	0.863
	4	1.18 (1.02-1.36)	0.026	1.06 (0.85-1.33)	0.601	1.14 (1.01-1.29)	0.03
	5 (least deprived)	1 (baseline group)		1 (baseline group)		1 (baseline group)	
Previous renal failure		3.48 (3.09-3.92)	<0.001	2.94 (2.48-3.50)	<0.001	2.37 (2.12-2.65)	<0.001
Type of Cancer	C17 - Malignant Neoplasm of Small Intestine	1.36 (1.07-1.73)	0.013	1.52 (1.07-2.15)	0.019	1.16 (0.94-1.44)	0.161
	C22 - Malignant Neoplasm of Liver and Intrahepatic Bile Ducts	1.26 (1.14-1.39)	<0.001	1.07 (0.91-1.26)	0.403	1.14 (1.04-1.24)	0.004
	C23 - Malignant Neoplasm of Gallbladder	1.30 (1.05-1.61)	0.018	1.09 (0.76-1.56)	0.639	1.18 (0.98-1.42)	0.077
	C24 - Malignant Neoplasm of other and unspecified parts of biliary tract	1.33 (1.09-1.61)	0.005	1.16 (0.86-1.57)	0.336	1.28 (1.08-1.52)	0.004
	C25 - Malignant Neoplasm of Pancreas	1 (baseline group)		1 (baseline group)		1 (baseline group)	
Previous ERCP		0.90 (0.82-0.99)	0.026	0.93 (0.80-1.08)	0.332	0.90 (0.83-0.97)	0.007

Procedural factors and mortality

The results of the multivariate regression analysis of procedural factors associated with mortality are shown in table 4. There was a five-fold variation in 30-day mortality between providers, ranging from 9.1% to 50%. Compared with providers undertaking 1-15 PTBDs per year, there was a significantly decreased in-hospital and 30-day mortality in providers performing 28 – 43 PTBDs per year (0.72 (95% CI 0.62-0.83), p<0.001 and 0.79 (95% CI 0.69-0.89), p<0.001 respectively). In providers performing more than 44 PTBDs per year, there was an even larger decrease in in-hospital (0.68 (95% CI 0.57-0.82), p<0.001), 7-day (0.54 (95% CI 0.40-0.74), p<0.001) and 30-day mortality 0.63 (95% CI 0.54-0.74), p<0.001). The effect of provider volume on 30-day mortality can be seen in figure 2.

The day of procedure had little influence on mortality with only Sunday having a higher in-hospital (2.54 (95% CI 1.66-3.91), p<0.001) and 30-day mortality (2.20 (95% CI 1.47-3.28), p<0.001) compared to Monday to Thursday. However, the number of patients who had a PTBD on a Sunday was very small at 114 (0.7%) and therefore these results should be treated with caution. In-hospital mortality post-PTBD on multivariate analysis fell over the period studied, with persistently lower in-hospital mortality between 2013 and 2014 (0.58 (95% CI 0.45-0.74), p<0.001) compared to 2001/2002.

Table 4 Multivariate regression analysis of procedural factors associated with mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease

		In-hospital mortality		7-Day Mortality		30-day mortality	
		Odds Ratio	P-value	Odds Ratio	P-value	Odds Ratio	P-value
PTBD Volume per year	≤15	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	16 to 27	0.79 (0.69-0.90)	0.001	0.92 (0.76-1.13)	0.44	0.93 (0.83-1.04)	0.218
	28 to 43	0.72 (0.62-0.83)	<0.001	0.81 (0.65-1.01)	0.063	0.79 (0.69-0.89)	<0.001
	44 to 83	0.68 (0.57-0.82)	<0.001	0.54 (0.40-0.74)	<0.001	0.63 (0.54-0.74)	<0.001
	84 to 180	0.68 (0.57-0.82)	<0.001	0.71 (0.52-0.95)	0.023	0.68 (0.58-0.79)	<0.001
Pancreaticoduodenectomy Volume	≤1	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	2 to 7	0.96 (0.84-1.11)	0.603	0.91 (0.73-1.12)	0.364	0.90 (0.80-1.01)	0.073
	8 to 23	1.08 (0.94-1.24)	0.278	0.97 (0.79-1.20)	0.79	0.99 (0.88-1.11)	0.814
	24 to 30	1.12 (0.93-1.35)	0.226	0.88 (0.66-1.18)	0.397	0.93 (0.80-1.09)	0.377
	30 to 86	1.01 (0.83-1.22)	0.96	0.87 (0.64-1.18)	0.371	0.95 (0.81-1.12)	0.549
Day of Procedure	Monday to Thursday	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	Friday	1.09 (0.99-1.20)	0.089	0.93 (0.79-1.09)	0.346	0.99 (0.91-1.08)	0.794
	Saturday	1.16 (0.78-1.71)	0.464	1.18 (0.64-2.16)	0.596	1.05 (0.75-1.48)	0.776
	Sunday	2.54 (1.66-3.91)	<0.001	3.69 (2.16-6.30)	<0.001	2.20 (1.47-3.28)	<0.001
	Bank Holiday or Bank Holiday Weekend	1.26 (0.98-1.61)	0.075	0.99 (0.65-1.51)	0.956	0.99 (0.79-1.25)	0.959
Year of PTC	2001/2	1 (baseline group)		1 (baseline group)		1 (baseline group)	
	2002/3	1.11 (0.86-1.44)	0.426	1.15 (0.75-1.76)	0.526	1.05 (0.84-1.31)	0.669
	2003/4	1.11 (0.85-1.45)	0.424	1.45 (0.96-2.19)	0.081	1.05 (0.84-1.31)	0.687
	2004/5	1.07 (0.82-1.38)	0.635	1.02 (0.66-1.58)	0.913	1.03 (0.83-1.29)	0.775
	2005/6	1.14 (0.88-1.47)	0.319	1.24 (0.83-1.87)	0.297	1.08 (0.87-1.34)	0.468
	2006/7	1.03 (0.80-1.33)	0.803	1.04 (0.69-1.58)	0.852	1.03 (0.83-1.27)	0.82
	2007/8	0.90 (0.70-1.16)	0.411	0.88 (0.58-1.33)	0.539	0.78 (0.63-0.97)	0.023
	2008/9	0.93 (0.73-1.19)	0.571	1.20 (0.81-1.78)	0.366	0.96 (0.78-1.19)	0.728
	2009/10	0.84 (0.66-1.08)	0.173	0.99 (0.67-1.47)	0.967	0.84 (0.68-1.03)	0.091
	2010/11	0.70 (0.55-0.90)	0.005	0.71 (0.47-1.07)	0.104	0.78 (0.63-0.96)	0.019
	2011/12	0.73 (0.57-0.94)	0.013	0.89 (0.60-1.33)	0.579	0.86 (0.70-1.05)	0.136
	2012/13	0.71 (0.56-0.91)	0.006	0.80 (0.54-1.19)	0.281	0.92 (0.75-1.13)	0.428
	2013/14	0.58 (0.45-0.74)	<0.001	0.71 (0.48-1.06)	0.094	0.65 (0.53-0.81)	<0.001

Repeat PTBD

The results of the multivariate analyses of factors associated with needing a further PTBD are shown in Table 5. Patients undergoing an additional PTBD procedure within 2 months of their initial PTBD were younger (81+ years, 0.21 (95% CI 0.16-0.27), p<0.001), less likely to have comorbidities (20+, 0.45 (95% CI 0.29-0.70), p<0.001) and were more likely to have cholangiocarcinoma (2.05 (95% CI 1.77-2.37), p<0.001). Patients undergoing their procedure in a high-volume centre performing between 84 and 180 procedures per year were much less likely to require a second procedure within 2 months (0.47 (95% CI 0.36-0.62), p<0.001). The majority of patients underwent a repeat PTBD in the same centre, with only 222 patients (22.1%) being referred to another provider. Repeat PTBD procedures were usually undertaken during emergency admissions (62.4%) rather than elective episodes (37.6%). 1,923 patients (11.4%) underwent an ERCP within 2 months of their initial PTBD.

Table 5 Multivariate regression analysis of factors associated with the need for a second percutaneous transhepatic biliary drainage for unresectable malignant disease

		Odds Ratio	P-value
Age Group	<61	1 (baseline group)	
	62 to 68	0.81 (0.68 - 0.97)	0.026
	69 to 74	0.67 (0.56 - 0.81)	<0.001
	75 to 80	0.50 (0.41 - 0.61)	<0.001
	81 +	0.21 (0.16 - 0.27)	<0.001
Sex	Male	1 (baseline group)	
	Female	0.84 (0.74 - 0.96)	0.01
Comorbidity Score	< 5	1 (baseline group)	
	5 to 10	0.86 (0.70 - 1.06)	0.161
	10 to 15	0.70 (0.59 - 0.83)	<0.001
	15 to 20	0.30 (0.20 - 0.45)	<0.001
	20+	0.45 (0.29 - 0.70)	<0.001
Spell Year	2001/02	1 (baseline group)	
	2002/03	1.07 (0.69 - 1.67)	0.757
	2003/04	1.00 (0.63 - 1.57)	0.997
	2004/05	0.94 (0.60 - 1.48)	0.803
	2005/06	0.91 (0.58 - 1.42)	0.664
	2006/07	1.32 (0.88 - 1.99)	0.186
	2007/08	1.24 (0.82 - 1.86)	0.308
	2008/09	1.52 (1.03 - 2.26)	0.035
	2009/10	1.78 (1.22 - 2.60)	0.003
	2010/11	1.57 (1.07 - 2.31)	0.022
	2011/12	1.99 (1.37 - 2.90)	<0.001
	2012/13	2.02 (1.39 - 2.94)	<0.001
	2013/14	1.91 (1.31 - 2.79)	0.001
Deprivation score	1 (most deprived)	0.78 (0.63 - 0.97)	0.023
	2	0.97 (0.79 - 1.19)	0.792
	3	0.94 (0.77 - 1.15)	0.543
	4	0.99 (0.81 - 1.21)	0.918
	5 (least deprived)	1 (baseline group)	
PTBD Volume per year	<=15	1 (baseline group)	
	16 to 27	0.72 (0.60 - 0.87)	0.001
	28 to 43	0.40 (0.32 - 0.50)	<0.001
	44 to 83	0.55 (0.42 - 0.72)	<0.001
	84 to 180	0.47 (0.36 - 0.62)	<0.001
Type of Cancer	C17 - Malignant Neoplasm of Small Intestine	1.47 (1.02-2.11)	0.038
	C22 - Malignant Neoplasm of Liver and Intraheptic Bile Ducts	2.05 (1.77-2.37)	<0.001
	C23 - Malignant Neoplasm of Gallbladder	1.68 (1.23-2.31)	0.001
	C24 - Malignant Neoplasm of other and unspecified parts of biliary tract	1.12 (0.77-1.63)	0.55
	C25 - Malignant Neoplasm of Pancreas	1 (baseline group)	

DISCUSSION

This is the largest study to date examining the outcomes of patients undergoing PTBD for unresectable malignant biliary tract obstruction. 7-day and 30-day mortality was 5.2% and 23.1% respectively with a median survival of 92 days. Reported 30-day mortality rates following PTBD vary considerably in the literature. In a 2008 review examining PTBD case series, 30-day mortality for patients with distal biliary obstruction varied from 2 to 20% and for hilar lesions from 9 to 20%, (2). However, 30-day mortality has been reported to be as high as 39% in other case series, (3, 12-14). In 2012, the results of a large UK audit of biliary drainage and stenting procedures were published. This showed an in-hospital mortality of 19.8% in those with malignant biliary obstruction, (15). Finally, a 2018 randomised controlled trial examining outcomes in patients with perihilar cholangiocarcinoma was stopped prematurely because of a higher mortality in the PTBD group compared to the endoscopic group (41 vs. 11%), (16).

Surgical or endoscopic drainage of the biliary system was not examined in the present study. Surgical drainage is associated with higher postoperative mortality and morbidity and an increased length of stay compared to non-surgical intervention, (17-20). The choice between endoscopic or percutaneous biliary drainage is less clear, as few randomized trials exist, (21). The decision often depends on the level of biliary obstruction. In England, PTBD is often the preferred technique for lesions above the common hepatic duct and when ERCP has failed, (8, 22). Endoscopic drainage, if technically possible, is probably perceived to be safer due to a small, very old, prospective randomized trial from 1987 in hilar and distal bile duct obstruction comparing the two techniques. The endoscopic approach had a higher success rate (81% vs. 61%, p=0.017) and a lower 30-day mortality (15% vs. 33%, p=0.016), (23). However, only plastic stents were used in this study, which does not reflect current practice. There is only one randomized trial comparing PTBD with ERCP in hilar biliary obstruction due to gallbladder cancer, (3). This demonstrated that PTBD had a higher success rate than ERCP (89% vs. 41%, $p < 0.001$) and a lower rate of early cholangitis (11% vs. 48%, $p = 0.02$). In a recent meta-analysis comparing PTBD with ERCP for the relief of malignant jaundice, patients undergoing PTBD were less likely to develop cholangitis compared to ERCP (0.55 (95% CI 0.36-0.84), p=0.006). However, there was no difference in success rate or 30-day mortality between the two approaches, (24).

The regression analysis in the present study identified patients with an increased risk of death post PTBD. Older males, with increasing deprivation and comorbidity (especially pre-existing renal dysfunction), and those with a cancer type other than pancreatic had a worse prognosis. Over 60% of patients in our cohort underwent a prior ERCP and this was expected, given that 62.5% of the patients had pancreatic or extra-hepatic cholangiocarcinoma. Undergoing an ERCP prior to PTBD was

associated with lower mortality. This likely to be due to a high proportion of those patients undergoing ERCP having pancreatic cancer, which carried a better prognosis. Patient fitness to undergo a second biliary drainage procedure was also a likely contributing factor. A reduced mortality in providers performing a higher volume of PTBDs each year was identified. A number of factors may contribute to this difference including variability in peri-procedural care such as antibiotics and post-procedure management of complications such as sepsis and renal failure. Higher volume centres may also have a more rigorous approach to patient selection, with a greater emphasis on careful multi-disciplinary team discussion of management prior to PTBD. We recognise that it is not realistic to expect all patients to be transferred to high volume centres for PTBD but the authors would recommend that PTBD outcomes are audited regularly and peri-procedural practices from high volume centres with good outcomes adopted in low volume centres.

Biliary obstruction in malignancy may result in pruritus, pain, cholangitis and liver failure, (1, 2). The goal of biliary drainage in inoperable patients is to improve quality of life and, in those with a good performance status, allow palliative chemotherapy. Two studies have shown that biliary drainage can improve quality of life, (3, 4) and it has been shown that gemcitabine-based combinations improve progression free survival in pancreatic cancer (HR 0.91 (95% CI 0.42-1.31), (5). A combination of gemcitabine and cisplatin can improve median survival in advanced biliary tract cancer from 8.1 to 11.7 months (HR 0.64 (95% CI 0.52 - 0.80), p<0.001), (6, 7). However, in our study, it is important to recognise that when considering PTBD, most patients did not receive chemotherapy after their procedure, with the rates decreasing significantly with age (aged <40 years (40.7% chemotherapy), aged 70 to 80 (17.4%), aged over 80 (2.5%)).

The rate of coded post-procedural complications in our study was high. 5.9% of patients were coded as experiencing a serious complication within 7 days, and 20.2% within 3 months. However, it was not possible to clarify the relationship between these later complications and the procedure or the underlying malignancy. Complication rates after PTBD vary between case series from 7 to 30%, (2), but cholangitis was common with rates of between 9 and 11% reported, (3, 12-14). The UK audit reported a minor complication rate of 26% and a major complication rate of 7.9%, including a 3.5% rate of sepsis, (16). It has therefore been recommended that all patients undergoing percutaneous drainage receive prophylactic antibiotics prior to their procedure, (25-28). However, there are no national or international guidelines to date on this issue. Rates of cholangitis in these studies were higher in patients with a low serum albumin or raised CRP, those with proximal or multiple points of intrahepatic biliary obstruction, neoplastic

invasion or compression of the duodenum and if Staphylococcus aureus was present at the site of skin puncture. With these factors in mind, patients should be monitored closely post-PTBD for early signs of sepsis, and infection treated aggressively with intravenous antibiotics and fluids. Stent occlusion due to the deposition of a bacterial biofilm and biliary sludge or tumour overgrowth is an important late complication, (29). In the present study, stent blockage or displacement was coded in 6.2% of patients and rates in other series have been reported at between 5 and 27%, (2, 30, 17). 13.5% of patients in the current study underwent more than one PTBD procedure. A 2008 review of PTBD series reported recurrence of obstructive jaundice in between 5 and 25% of patients, with the majority undergoing a repeat PTBD, (2).

Every healthcare provider in England is required to submit diagnostic and procedural data to HES. However, the accuracy of the coding data submitted is a potential concern as it depends on the quality of the medical records and on the staff coding the records. HES produces a yearly report on the quality of the data received. In the 2012/2013 report, 99.3% of primary diagnoses and 99.9% of primary procedure codes were accurate, (31). In order to validate the accuracy of diagnostic and procedural coding relevant to the present study, the number of PTBDs meeting the study criteria at UHB between 2009 and 2014 was compared to the number submitted to HES. 321 patients were recorded in HES as undergoing PTBD at UHB and 305 patients were identified from examining local radiology data, giving an accuracy of 95%. HES data is unfortunately not linked to cancer registry data, due to restrictions under which the data is held. Patients were therefore excluded who had very long periods following an apparent diagnosis of malignancy and PTBD and those with long delays in cancer diagnosis following PTBD. There are some important aspects of the patient's care that are not recorded in HES. Information regarding the exact location of the lesion, the precise technique used (such as use of external drainage or type of stent placed) and whether the procedure was performed with ultrasound guidance, by a supervised trainee, or by an experienced interventional radiologist was not available. Important data such as whether any technical difficulties were encountered, performance status, bilirubin and albumin levels, clotting profile or inflammatory markers were also not available. In particular, prescription data regarding antibiotic use is not recorded, which limits our ability to investigate further the high frequency of septic complications. Recording of chemotherapy in HES may also not be entirely complete, (31).

In conclusion, 30-day mortality in patients undergoing PTBD for relief of unresectable malignant biliary obstruction was high at 23.1%. Older males and those with increasing comorbidity (especially pre-existing renal dysfunction) and

deprivation have a poorer prognosis. Patients undergoing a PTBD in a provider that performs more than 28 procedures per year have a significantly lower risk of death and there is a large variation in outcomes between providers. In light of the high mortality found in this study, the authors strongly recommend that patients undergo careful multi-disciplinary discussion prior to PTBD in order to identify risk factors for a poor outcome, to treat renal dysfunction and sepsis early, and to confirm that the patient is likely to benefit from PTBD, in terms of either symptom relief or as a bridge to chemotherapy.

Acknowledgements

The authors would like to acknowledge the contribution of Mr. Keith Roberts, consultant hepato-biliary surgeon at University Hospital Birmingham, with identifying relevant surgical procedures.

Author contributions:

James Rees: First author, study concept and design, data interpretation, drafting of manuscript
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Felicity Evison: Acquisition of data, data analysis
Kamarjit Singh Mangat: Study concept and design, critical revision of manuscript for important intellectual content
Prashant Patel: Study concept and design, data interpretation, critical revision of manuscript for important intellectual content
Nigel Trudgill: Senior author, study concept and design, data interpretation, drafting of manuscript, study supervision

Funding:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Conflict of interests:

Kamarjit Singh Mangat is the inventor of a biliary biopsy forceps kit that was first licensed in 2013. The rights have been transferred to Cook Medical and he receives minimal royalties for sales of this device.

Data Availability Statement:

All data relevant to the study are included in the article or uploaded as supplementary information

Figure 1 Study Flowchart

Figure 2 Kaplan Meier unadjusted analysis of 30-day mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease by provider volume

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Figure 1 Study Flowchart

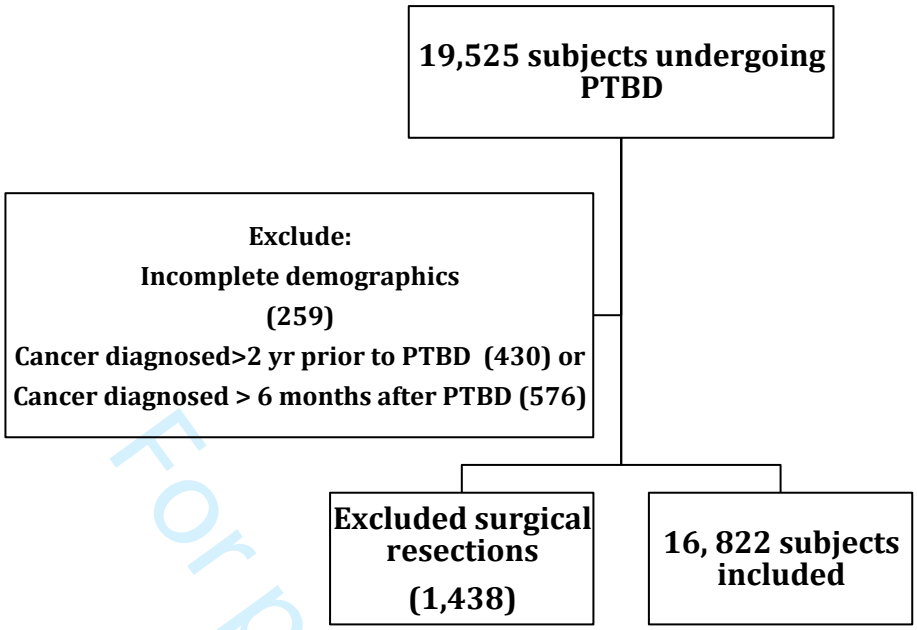
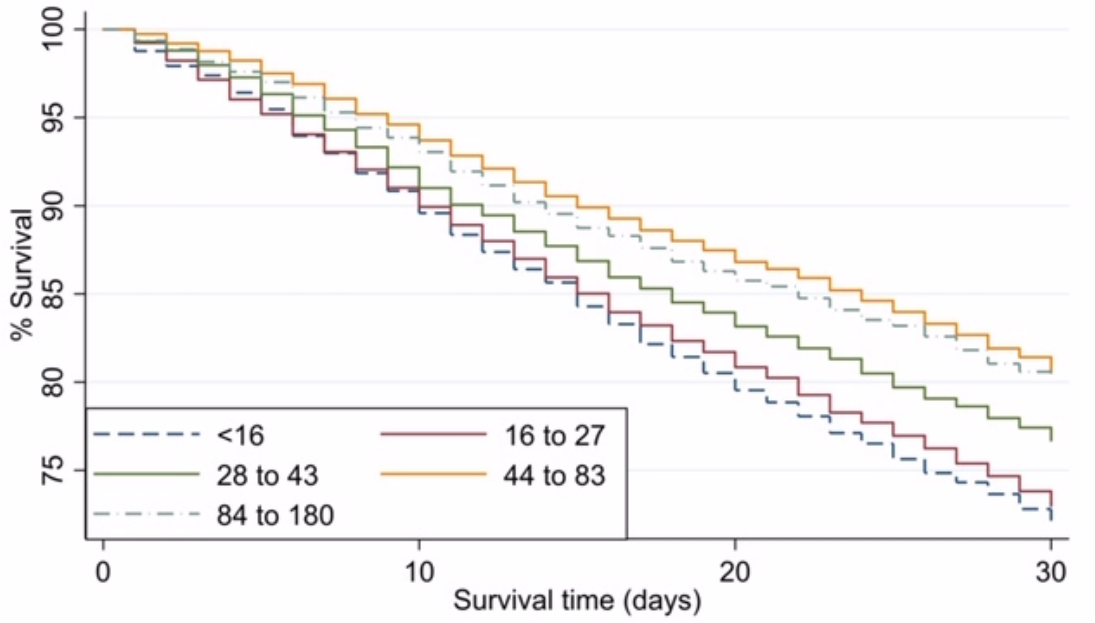


Figure 2 Kaplan Meier unadjusted analysis of 30-day mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease by provider volume



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	5, 6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-7
		(*b*) Describe any methods used to examine subgroups and interactions	5-7
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-13
Limitations			13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.