

PEER REVIEW HISTORY

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ARTICLE DETAILS

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| TITLE (PROVISIONAL) | 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 |
| AUTHORS | Rees, James; Mytton, Jemma; Evison, Felicity; Mangat, Kamarjit; Patel, Prashant; Trudgill, Nigel |

VERSION 1 – REVIEW

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| REVIEWER | Yousuke Nakai The University of Tokyo, JAPAN |
| REVIEW RETURNED | 17-Aug-2019 |

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| GENERAL COMMENTS | <p>This is a retrospective study of PTBD for malignant biliary obstruction using Hospital Episode Statistics in England. The study revealed a relatively high 30-day mortality rate (23.1%) and its risk factors. The strength of this study was its sample size and validation using a hospital based data. However, treatment selection between PTBD and ERCP is clinically important.</p> <ol style="list-style-type: none">1. As the authors discussed, the strength of this study is its sample size. To make the best of this study strength, I would strongly recommend a comparison of PTBD vs. ERCP-based biliary drainage, rather than a single arm study. As described in the paper, treatment selection between PTBD vs. ERCP is clinically more relevant such as morbidity, mortality and hospital stay. Although there is tendency that PTBD is selected for hilar biliary obstruction, I believe the comparison can be adjusted using a propensity score matched analysis.2. In a real world, patients who underwent PTBD in a low volume center without clinical response would sometimes be referred to a high volume center. Can this database follow the patient referral and analyze similar to repeat PTBD in the same hospital?3. Are there any cases who underwent ERCP after the initial PTBD?4. There are numerous analyses in this study. Bonferroni correction might be necessary.5. The authors revealed risk factors for 30-day mortality but most of risk factors cannot be intervened. The only factor which can be intervened is the hospital volume. Based on the study results, do the authors recommend PTBD at a high volume center alone?6. Mortality rate was relatively high. I am very curious whether this was PTBD-related or disease progression.7. The authors mentioned about antibiotics. It would be interesting if the authors can include data on antibiotics as well as bile/blood culture data in the analysis.8. Figure 2 showed a cumulative survival curves within 30-days. K-M curve of 30-day mortality was not appropriate. |
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| REVIEWER | CHJ van Eijck ErasmusMC The Netherlands |
| REVIEW RETURNED | 18-Aug-2019 |

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| GENERAL COMMENTS | <p>Thank you for the opportunity to review to interesting and important paper. It gives a good reflection of daily clinical practice on an important issue, obstructive jaundice in patients with mainly inoperable HPB tumor. I just have a view comments to make.</p> <ol style="list-style-type: none"> 1. I personally would prefer to consider the subjects to be patients, I think this is more respectful 2. In the discussion I would like the authors to comment on the fact that more than 60% of all patients first had an ERCP. This I find extremely high since nowadays most patients undergo an Endoscopic Ultrasound as well. When the scope could not enter the duodenum, why an ERCP would be an option than? 3. In the discussion the authors should mention the paper of Coelen at all Lancet Gastroenterology Hepatology 2018 Oct 3(10) 681-690. The study was prematurely stopped because of higher all-cause mortality in the percutaneous transhepatic biliary drainage group. 4. Could the authors comment what should be the best procedure of drain placement in these patients. First external drainage for a couple of days followed by internal drainage or direct passage into the duodenum or even direct stent placement. This could be an important issue to explain the high mortality. |
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| REVIEWER | Debin Wang School of Health Services Management, Anhui Medical University, China |
| REVIEW RETURNED | 03-Sep-2019 |

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| GENERAL COMMENTS | <p>The paper documents interesting findings on mortality rates among nearly 20 thousand patients underwent PTBD and their associations with social economic status and clinical complications and procedures. The manuscript is well written and is publishable with minor revisions.</p> <p>Being invited as a statistical reviewer, I'd like to say that the methods used in the data analysis are generally sound. Given the large numbers of variables included in the analysis, it is reasonable to use "univariate analysis to identify variables to be included in the final regression models".</p> <p>The authors performed multivariate regression modeling for identifying factors associated with repeated PTBD but only very simple descriptive analysis for factors associated with pre- and post-PTBD chemotherapy. Given the data available, I'd suggest the authors perform the same multiple variate regression analysis for all the three procedural variables.</p> <p>The title of table 5 reads "Multivariate regression analysis of demographic factors associated with the need for a second percutaneous transhepatic biliary drainage for unresectable malignant disease". But, as shown in the table, the regression model includes not only demographic factors (e.g., age group, sex) but also health conditions and clinical factors (e.g., comorbidity score, type of cancer, spell year). I'd suggest reword the title to cover all the</p> |
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| | <p>factors included.</p> <p>The discussion focuses mainly on comparing the findings from the authors' own study and that from the literature. It may help the readers better understand the study, if the discussion includes some interpretations/explanations of the key findings, e.g., why providers with greater PTBD volume were found with lower mortality.</p> |
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| REVIEWER | Eoin Slattery University Hospital Galway |
| REVIEW RETURNED | 13-Sep-2019 |

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| GENERAL COMMENTS | <p>Interesting and well written study that adds valuable data to the established literature.</p> <p>Some points:</p> <ul style="list-style-type: none"> -perhaps the most practice changing aspect of this study is outcomes by volume of PTBD provider, for this reason a Kaplan Meier of outcomes by numbers of PTBD performed should be provided (in lieu of the age graph presented) -the proportion of patients undergoing PTBD with panc cancer seems proportionately high? How many of this cohort had attempt at previous ERCP. This should be high, if not why was PTBD preferred first line, ?lack of available expertise?? Does this bias results? -Previous ERCP was protective which doesn't make sense intuitively. Why was this?? Does the underlying disease make a difference here? -Previous failed ERCP leading to PTBD in complex cholangio likely leads to more complications, was this observed? Partic with respect to infections -Previous ERCP described was during the same admission or at a different time?? i.e. was PTBD provided for salvage reasons post failed ERCP or due to progression of underlying disease. -Is ERCP volume available with this dataset to compare outcomes? -Is it possible to capture what type of PTBD was performed i.e. placement of int-ext catheters, stenting etc -Can this dataset capture planned day case activity e.g. planned tube changes, interval stenting etc or only emergency admissions? -Does hospital site make a difference i.e. university/academic vs DGH. Are PTBD numbers provided for the institution or per physician |
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Yousuke Nakai

Institution and Country: The University of Tokyo, JAPAN

Please state any competing interests or state 'None declared': None

This is a retrospective study of PTBD for malignant biliary obstruction using Hospital Episode Statistics in England. The study revealed a relatively high 30-day mortality rate (23.1%) and its risk factors. The strength of this study was its sample size and validation using a hospital based data. However, treatment selection between PTBD and ERCP is clinically important.

1. As the authors discussed, the strength of this study is its sample size. To make the best of this

study strength, I would strongly recommend a comparison of PTBD vs. ERCP-based biliary drainage, rather than a single arm study. As described in the paper, treatment selection between PTBD vs. ERCP is clinically more relevant such as morbidity, mortality and hospital stay. Although there is tendency that PTBD is selected for hilar biliary obstruction, I believe the comparison can be adjusted using a propensity score matched analysis.

Thank you for this suggestion. Unfortunately, we have not been able to examine ERCP data in detail this study and are therefore unable to potentially compare outcomes between the two approaches. We would have some concerns about this comparison and the propensity score matching the reviewer proposes, as PTBD and ERCP are generally undertaken for different levels of biliary obstruction and cancer types, with different outcomes and responses to chemotherapy, affecting outcomes. (Text not amended).

2. In a real world, patients who underwent PTBD in a low volume centre without clinical response would sometimes be referred to a high volume centre. Can this database follow the patient referral and analyze similar to repeat PTBD in the same hospital?

Thank you for this helpful suggestion. We have examined this issue and only 22.1% of patients underwent their second PTBD in a different centre. We have not undertaken a separate analysis for patients undergoing a PTBD in a different centre due to the low number of patients involved. Text amended on page 17: '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%).'

3. Are there any cases who underwent ERCP after the initial PTBD?

Thank you for this question. 15.5% of patients underwent an ERCP after their original PTBD. Text amended on page 17: '1,923 patients (11.4%) underwent ERCP within 2 months of their initial PTBD.'

4. There are numerous analyses in this study. Bonferroni correction might be necessary.

Thank you for this helpful comment. We have re-examined the data and found that Bonferroni correction would apply to the Univariate analyses examining included and excluded patients and factors affecting chemotherapy (Tables 1 and 2 respectively). We have applied this to the analyses and found that the results have not changed but that they can only be considered statistically significant if $p < 0.0045$. Text amended on page 7: '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 .'

5. The authors revealed risk factors for 30-day mortality but most of risk factors cannot be intervened. The only factor which can be intervened is the hospital volume. Based on the study results, do the authors recommend PTBD at a high volume centre alone?

Thank you for asking this important question. We have demonstrated that outcomes are significantly worse in low-volume providers. We recognise that all patients undergoing PTBD in high volume providers would be likely to lead to unacceptable delays in treatment for many patients, as well as significant pressures on high-volume providers. We do, however, suggest a standardised approach to pre and post-procedure management for these patients, with low-volume providers adopting the practices of higher-volume centres with good outcomes. We had discussed this on page 19 but have

expanded this so that it is clearer.

Text amended and discussion now reads '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 e.g. antibiotics and 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 higher volume centres for PTBD but the authors would recommend that PTBD outcomes are audited regularly and practices from high volume centres with good outcomes adopted in low volume centres'.

6. Mortality rate was relatively high. I am very curious whether this was PTBD-related or disease progression.

Thank you for raising this important question. This is almost certainly due to a combination of the two factors mentioned by the reviewer. By definition, these patients have advanced, inoperable disease and will have a limited prognosis. The observed mortality in our paper is comparable to the inpatient mortality seen in the referenced British Society of Interventional Radiology: biliary drainage and stenting registry (BDSR), (15). As we have no access to detailed records of inpatient care, it not possible to comment further on the relative proportion of patients dying of their disease rather than as a direct result of the procedure. This is a limitation of HES data and we have acknowledged this on page 19 of the discussion 'However, it was not possible to clarify the relationship between these later complications and the procedure or the underlying malignancy' (text not amended).

7. The authors mentioned about antibiotics. It would be interesting if the authors can include data on antibiotics as well as bile/blood culture data in the analysis.

Thank you for making this suggestion. Unfortunately, data regarding the prescription of antibiotics and pathology/microbiology results are not recorded in HES. We have highlighted this in the discussion (page 20), in the paragraph discussing the limitations of HES. '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' (text not amended).

8. Figure 2 showed a cumulative survival curves within 30-days. K-M curve of 30-day mortality was not appropriate.

Thank you for this helpful suggestion. We have removed Figure 2 from the paper and supplied it as supplementary material (Supplementary Figure 1). As suggested by another reviewer, we have replaced it with a Kaplan Meier for 30-day mortality following PTBD by provider volume.

Text amended on page 21: 'Figure 2 Kaplan Meier unadjusted analysis of 30-day mortality following percutaneous transhepatic biliary drainage for unresectable malignant disease by provider volume'. We have also supplied a Kaplan Meier for 24-month mortality by provider volume (Supplementary Figure 2).

Reviewer: 2

Reviewer Name: CHJ van Eijck

Institution and Country: ErasmusMC, The Netherlands

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the opportunity to review to interesting and important paper. It gives a good reflection of daily clinical practice on an important issue, obstructive jaundice in patients with mainly inoperable HPB tumor.

I just have a view comments to make.

1. I personally would prefer to consider the subjects to be patients, I think this is more respectful

Thank you for this suggestion. We have changed to patients throughout the manuscript, as suggested. Text amended.

2. In the discussion I would like the authors to comment on the fact that more than 60% of all patients first had an ERCP. This I find extremely high since nowadays most patients undergo an Endoscopic Ultrasound as well. When the scope could not enter the duodenum, why an ERCP would be an option than?

ERCP is considered to be the biliary drainage procedure of choice in pancreatic and extra-hepatic bile duct neoplasms. 58% of our patients had pancreatic cancer and 4.5% had extra-hepatic bile duct cancer. Therefore, we feel that 61.8% of our patients undergoing a prior ERCP is an expected result.

Text amended on page 18 'Over 60% of patients in our cohort underwent a prior ERCP and this was to be expected, given that 62.5% of the patients had pancreatic cancer or extra-hepatic cholangiocarcinoma.'

3. In the discussion the authors should mention the paper of Coelen at al Lancet Gastroenterology Hepatology 2018 Oct 3(10) 681-690. The study was prematurely stopped because of higher all-cause mortality in the percutaneous transhepatic biliary drainage group.

Thank you for drawing our attention to this important study. Text amended on page 18: '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).'

4. Could the authors comment what should be the best procedure of drain placement in these patients? First external drainage for a couple of days followed by internal drainage or direct passage into the duodenum or even direct stent placement. This could be an important issue to explain the high mortality.

Thank you for highlighting this important technical issue. Unfortunately, one of the limits of HES data, is that it does not give sufficient procedural data to establish whether external drainage, internal drainage or direct stent insertion are associated with better outcomes. OPCS 4 codes do exist which describe the PTBD in more detail. For example, there are codes for insertion of tubal prostheses into the right or left hepatic ducts, as well as the common bile duct (see appendices). However, we found that these codes were rarely used and it was much more likely that the procedure would be coded more generically as 'Percutaneous transhepatic cholangiography'. There is no code for placement of an external drain and these procedures would receive a generic PTBD code.

Text amended (page 20): 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 placement of an external drain 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.

Reviewer: 3

Reviewer Name: Debin Wang

Institution and Country: School of Health Services Management, Anhui Medical University, China

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

The paper documents interesting findings on mortality rates among nearly 20 thousand patients underwent PTBD and their associations with social economic status and clinical complications and procedures. The manuscript is well written and is publishable with minor revisions.

Being invited as a statistical reviewer, I'd like to say that the methods used in the data analysis are generally sound. Given the large numbers of variables included in the analysis, it is reasonable to use "univariate analysis to identify variables to be included in the final regression models".

The authors performed multivariate regression modeling for identifying factors associated with repeated PTBD but only very simple descriptive analysis for factors associated with pre- and post-PTBD chemotherapy. Given the data available, I'd suggest the authors perform the same multiple variate regression analysis for all the three procedural variables.

Thank you for this suggestion. As PTBD is often performed to facilitate palliative chemotherapy, we have examined the proportion of patients undergoing this post PTBD. We found, as expected, a significant reduction in chemotherapy by age and variation in rates by cancer type. There was also an expected increase in chemotherapy with time. We have chosen not to undertake logistic regression analysis of chemotherapy as the most important clinical determinant of suitability for chemotherapy is performance status and these data were unfortunately not available to us (text not amended).

The title of table 5 reads "Multivariate regression analysis of demographic factors associated with the need for a second percutaneous transhepatic biliary drainage for unresectable malignant disease". But, as shown in the table, the regression model includes not only demographic factors (e.g., age group, sex) but also health conditions and clinical factors (e.g., comorbidity score, type of cancer, spell year). I'd suggest reword the title to cover all the factors included.

Thank you for highlighting this. Text amended (Page 17): the title of table 5 now reads 'Multivariate regression analysis of factors associated with the need for a second percutaneous transhepatic biliary drainage for unresectable malignant disease'

The discussion focuses mainly on comparing the findings from the authors' own study and that from the literature. It may help the readers better understand the study, if the discussion includes some interpretations/explanations of the key findings, e.g., why providers with greater PTBD volume were found with lower mortality.

We are grateful for this comment and have altered the text of the discussion to give our interpretation of why mortality is higher in low-volume centres. Text amended (Page 19): '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

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 but the authors would recommend that PTBD outcomes are audited regularly and practices from high volume centres with good outcomes adopted in low volume centres.'

Reviewer: 4

Reviewer Name: Eoin Slattery

Institution and Country: University Hospital Galway

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Interesting and well-written study that adds valuable data to the established literature.

Some points:

Perhaps the most practice changing aspect of this study is outcomes by volume of PTBD provider, for this reason a Kaplan Meier of outcomes by numbers of PTBD performed should be provided (in lieu of the age graph presented)

Thank you for this helpful comment. We have replaced the original age graph with a Kaplan Meier of 30-day mortality by provider volume (Figure 2). Text amended on page 14: 'The effect of provider volume on 30-day mortality can be seen in figure 2.' We have also included a Kaplan Meier of 2-year mortality by provider volume and included it in the supplementary material (Supplementary Figure 2). The original age graph has also been included in the supplementary materials (Supplementary Figure 1).

The proportion of patients undergoing PTBD with panc cancer seems proportionately high? How many of this cohort had attempt at previous ERCP? This should be high, if not why was PTBD preferred first line,? lack of available expertise?? Does this bias results?

Thank you for this question. The proportion of patients with pancreatic cancer undergoing ERCP prior to PTBD is indeed high at 67.5%. Unfortunately, we did not have access to detailed records of inpatient care and it is not possible to determine why approximately 30% of patients with pancreatic cancer did not undergo prior ERCP. It is likely that this is due to patient factors, such as duodenal obstruction, rather than lack of access to ERCP, as this is available in all hospitals in England (text not amended).

Previous ERCP was protective which doesn't make sense intuitively. Why was this?? Does the underlying disease make a difference here?

Thank you for raising this important point. 58% of patients in our cohort had a diagnosis of pancreatic cancer and 67.5% of these patients underwent an ERCP prior to PTBD. We have demonstrated that these patients carry a better prognosis in our multivariate analysis. It is very likely that only patients who have a better performance status are likely to be fit to undergo another later drainage procedure. A combination of these two factors is likely to explain why a previous ERCP is protective.

Text amended (Pages 18-19): 'Undergoing an ERCP prior to PTBD was associated with lower mortality. This is likely to be due to a high proportion of those patients having pancreatic cancer, which carried a better prognosis. Patient fitness to undergo a second procedure is also a likely

contributing factor.'

Previous failed ERCP leading to PTBD in complex cholangio likely leads to more complications, was this observed? Partic with respect to infections

This is an interesting point, and it is confirmed in our data. Those with cholangiocarcinoma undergoing ERCP prior to PTBD had a slightly higher rate of complications (20.5 vs. 19.6%). Rates of cholangitis were higher in the prior ERCP group (4.1 vs 3.5%), as was stent occlusion (3.2 vs 2.4%) (text not amended).

Previous ERCP described was during the same admission or at a different time?? i.e. was PTBD provided for salvage reasons post failed ERCP or due to progression of underlying disease.

Thank you for this question. 57.9% of patients had an ERCP followed by a PTBD on the same admission. It is therefore likely that the PTBD was a salvage procedure in these patients. The remainder are likely to have had a repeat procedure due to disease progression. Text amended (Page 8): '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.'

Is ERCP volume available with this dataset to compare outcomes?

Thank you. Unfortunately, we have not had the opportunity to examine ERCP volume in our cohort, as the focus of our study was PTBD not ERCP (text not amended).

Is it possible to capture what type of PTBD was performed i.e. placement of int-ext catheters, stenting etc

Thank you for raising this important issue. OPCS 4 codes do indeed exist which describe the PTBD in more detail. For example, there are codes for insertion of tubal prostheses into the right or left hepatic ducts, as well as the common bile duct (see appendices). However, we found that these codes were rarely used and it was more likely that the procedure would be coded more generically as 'Percutaneous transhepatic cholangiography'. There is no code for placement of an external drain, rather these procedures would receive a generic PTBD code as detailed above. Therefore, we are not able to confidently comment on the type of PTBD performed.

Text amended (page 20): 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 placement 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.

Can this dataset capture planned day case activity e.g. planned tube changes, interval stenting etc or only emergency admissions?

HES captures both elective and emergency admissions to secondary care. 'Repeat PTBD procedures were usually undertaken during emergency admissions (62.4%) rather than elective episodes (37.6%)' (Text amended on page 16).

Does hospital site make a difference i.e. university/academic vs DGH. Are PTBD numbers provided for the institution or per physician?

Thank you for this interesting question. We would have liked to be able to examine outcomes at an individual medical practitioner level but this is not possible in HES. It is also unfortunately not possible to distinguish between University Hospitals and District General Hospitals with HES codes alone, although it is likely that the higher volume providers are tertiary university centres (text not amended).