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Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study

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ABSTRACT

Background: Pancreatic exocrine insufficiency (PEI) and malnutrition are prevalent among patients with pancreatic adenocarcinoma. Pancreatic enzyme replacement therapy (PERT) can correct PEI but its use among patients with pancreatic cancer is unclear as are effects upon survival. This population-based study sought to address these issues

Methods: Subjects with pancreatic adenocarcinoma were identified from the UK Clinical Practice Research Datalink (CPRD). Propensity score matching generated matched pairs of subjects who did and did not receive PERT. Progression to all-cause mortality was compared using parametric survival models that included a range of relevant co-variables

Results: PERT use among the whole cohort (987/4554) was 21.7%. Some 1614 subjects generated 807 matched pairs. This resulted in a total, censored follow-up period of 1643 years. There were 1403 deaths in total, representing unadjusted mortality rates of 748 and 994 deaths per 1000 person-years for PERT-treated cases and their matched non-PERT-treated controls, respectively. With reference to the observed survival in pancreatic adenocarcinoma patients, adjusted median survival time was 262% greater in PERT-treated cases (survival time ratio (STR) = 2.62, 95% CI 2.27–3.02) when compared with matched, non-PERT-treated controls. Survival remained significantly greater among subjects receiving PERT regardless of the studied subgroup with respect to use of surgery or chemotherapy

Conclusions: This population based study observes that the majority of patients with pancreatic adenocarcinoma do not receive PERT. PERT is associated with increased survival among patients with pancreatic adenocarcinoma suggesting a lack of clinical awareness and potential benefit of addressing malnutrition among these patients

Introduction

The outlook among patients with pancreatic ductal adenocarcinoma (PDAC) is very poor. Despite advances in chemotherapeutics [1] and organised systems for the delivery of specialist care [2] the 5 and 10 year survival among these patients has not improved over the past 40 years [3]. Surgery offers a chance of cure though without chemotherapy 5 year survival is under 10% [4]. When surgery is not possible median survival is measured in months [5]. Despite these stark data there is evidence that improvement is possible. The recent ESPAC 4 study has estimated a 28% five year survival following surgery among those receiving adjuvant combination chemotherapy [1] and among patients with unresectable disease FOLFIRINOX chemotherapy almost doubles the median survival compared to gemcitabine [5]. Despite the advantages population based studies show that between one quarter and one half of patients never receive any form of adjuvant therapy following surgery [6] and less than 20% of patients with metastatic cancer receive palliative chemotherapy [7].

The reasons for poor outcomes and undertreatment with chemotherapy are multifactorial. The disease is rapidly progressive [8]; patients are typically elderly and many lack capacity to undergo major surgery and/or tolerate chemotherapy [9].

At presentation malnutrition is prevalent among these patients and will contribute to frailty due to high metabolic demands related to the cancer burden [8]. This drives cachexia and anorexia

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which compounds problem [10] which in turn reduces a person's ability to undergo surgery or receive chemotherapy. Treatment of malnutrition, in general, is essential to ensure that patients with cancer undergo and recover from treatment such as major surgery and adjuvant or palliative chemotherapy. Pancreatic exocrine insufficiency (PEI) is an additional and fundamental cause of malnutrition among the majority of patients with resectable [11] and unresectable [12] PDAC. Mechanisms of PEI among these patients include obstruction of the pancreatic duct, fibrosis of the gland and loss of pancreatic exocrine tissue and for some patient's surgical removal of part or all the gland [11]. Furthermore, the main stimulus for pancreatic secretion is mediated by the duodenum, an effect lost among the majority of patients undergoing surgery. Finally, enzyme function is dependent upon neutral luminal pH; reduction or obstruction of bicarbonate secretion from the pancreas further contributes to malabsorption due to effects of unopposed gastric acid [13]. PEI manifests itself as various gastrointestinal symptoms as well as failure to absorb nutrients and essential vitamins [14]. At presentation this results in weight loss, steatorrohoea [15], micronutrient deficiency and impaired quality of life [11]. The degree of weight loss correlates with reduced survival in this setting [16]. Pancreatic enzyme replacement therapy (PERT) is the only treatment for PEI.

Despite the prevalence of PEI among patient with PDAC there is evidence that the majority of patients do not receive treatment with PERT [17]. There is evidence from single centre studies that treating PEI among patients with chronic pancreatitis [18] and periampullary malignancy [19] improves survival. There is however, a clear paucity of data in this field and single centre studies may suffer from various biases and confounding.

This study presents a population-based analysis of survival among patients with PDAC stratified by use of PERT or not. The primary aim was to identify whether PERT use was associated with increased survival. Secondary aims included identifying the frequency of PERT use among these patients and association of other variables with survival.

Methods

This was a retrospective population based observational cohort study among patients diagnosed with PDAC using propensity matched analysis.

Data was obtained from the Clinical Practice Research Datalink (CPRD) and linked data from the Office for National Statistics (ONS) and Hospital Episode Statistics (HES) in England. Ethical approval for the study was granted by the CPRD Independent Scientific Advisory Committee on 29 June 2016, protocol number 16_124.

Data source

The CPRD observational dataset consists of longitudinal, anonymous records from over 700 primary care practices classified as being of research quality comprising over 14 million patients throughout the U.K. (based on the Sep 2016 release) [20]. The computerised data, recorded in the course of routine health care by general practitioners (GPs) and associated staff, include demographic and lifestyle information, medical history, clinical investigations, drug prescriptions, and hospital referrals. Diagnoses in CPRD are recorded using the Read code classification and have been validated in a number of studies, showing a high positive predictive value [21].

Some 404 of the English practices contributing to the dataset, representing 56% of CPRD patients, are linked to the HES and Office of national statistics databases for mortality. HES provides details of all National Health Service (NHS) inpatient admissions in England since 1997, including primary and contributory causes coded using the ICD-10 classification [22]. ONS provides details of all deaths in England, with immediate and antecedent causes coded using the ICD- 9 and ICD-10 classifications [23].

Definition of investigated variables

Patients were defined as incident PERT cases based on a period of observation of least 365 days from start of their CPRD record to first observed PERT prescription. The index date was PDAC presentation date, defined as the date of first recorded diagnosis of PDAC. Patients were followed until death or end of follow up.

Patients undergoing surgery (pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy) within a 180 day period before or after diagnosis were identified using relevant OPCS codes. Receipt of chemotherapy was identified among patients following a diagnosis of PDAC. Chemotherapy given prior to the diagnosis or prior to surgery was considered not related to the diagnosis of PDAC. It is to be noted that the timeframe of the current study precedes use of neoadjuvant therapy for PDAC.

Other variables studied include age, gender, socio-economic status (quintiles of Index of Multiple Deprivation), self-assigned ethnicity, index year, smoking status, Charlson co-morbidity index [24], +/− chemotherapy, +/− pancreaticoduodenectomy surgery, +/− total pancreatectomy surgery, +/− distal or partial resection surgery, and case/control status.

The following variables were considered potentially important but not studied because of large proportions of missing data: body mass index (BMI), systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and creatinine clearance. However, major adverse cardiac events and other co-morbidity are components of the Charlson index.

Patient selection and matching

Patients were selected if diagnosed with pancreatic ductal adenocarcinoma (PDAC) using Read and ICD-10 coding and registered with practices between Jan 1998 and Sep 2015. Those patients were then stratified into those receiving PERT or not, during the study period.

Patients were classified as PERT-treated cases if they were initiated on PERT on or after their PDAC presentation date. PDAC presentation and PERT initiation dates were defined as the first observed date of PDAC diagnosis and PERT prescription, respectively. A minimum period for 365 days from registration to first observed PDAC diagnosis was applied to exclude non-incident PDAC (n = 372). Similarly, patients were excluded if they had any record of either acute or chronic pancreatitis as these patients may have had preexisting PERT therapy (n = 952). Otherwise patients were classified as non-PERT-treated controls if they had no recorded prescription of PERT.

In order to improve ascertainment of events, only patients linked to HES and ONS mortality datasets were included, with the former providing details of diagnoses and procedures related to inpatient episodes, and the latter providing both the date and cause(s) of death. Furthermore, patients with implausible or improbable dates were excluded (n = 539).

PERT-treated cases were propensity score matched to non-PERT-treated subjects with PDAC, at a 1:1 ratio. The propensity scores were formulated by fitting a logistic regression model, which predicted case versus control, using the following covariates: age at index, gender, socioeconomic status, calendar year of index date, Charlson Comorbidity Index (CCI) score, +/− chemotherapy, and±pancreaticoduodenectomy (PD) surgery (within 6 months

before/after diagnosis of PDAC). Table S1 summarises the steps used to identify the studied cohorts.

The propensity scores were used to match cases to controls, using exact (or forced) matching for±chemotherapy and±pancreaticoduodenectomy covariates, and within a caliper of 0.2 standard deviations for all other covariates.

Study endpoint

The study endpoint was all-cause mortality.

Statistical methods

Continuous baseline characteristics were compared between subgroups using the independent samples *t*-test or Mann-Whitney *U* test depending on their distribution. Categorical variables were compared using the chi-square test. Differences in survival in Kaplan-Meier analysis were compared using the log-rank test.

Variables defined above were selected as the candidate covariates for analysis. All categorical variables were treated as discrete and converted to binary variables with the exception of index year and Charlson index. Interaction effects between study arm and all other candidate covariates were considered.

Modelling of survival in the matched cohort was not performed with a Cox proportional hazards model because the proportional hazards assumption was violated. We therefore fitted a parametric accelerated failure time survival model. Weibull, log-normal and log-logistic models were assessed for goodness-of-fit using the Akaike information criterion (AIC) [25]. The log-logistic model resulted in the best fit in terms of AIC, and the adequacy of this distribution was further assessed by plotting appropriately transformed non-parametric estimates against time. The log-logistic survival model provides beta coefficients that equal the difference in log survival time between groups or for continuous predictors. Exponentiation of the beta coefficient gives the ratio between median survival times, known as the survival time ratio (STR), or acceleration factor. STRs less than 1 represent a decrease in survival time; values greater than 1 represent prolonged survival.

From the pool of candidate covariates a reduced model was obtained by applying a backwards selection procedure, with AIC as the stopping criterion.

Extensive subgroup analyses are reported using the final model to test its robustness. To evaluate potential effects of immortal time bias model variants 1–3 excluded patients that died within 30-, 60-, or 90- days of index, respectively.

All statistical analyses were carried out using R (version 3.3.2). CB performed the statistical analyses; all authors were involved in study design and interpretation of data. Funding for this study was provided by Mylan pharmaceuticals. However, neither Mylan nor its employees, had any role in study design, data acquisition, and analysis or manuscript preparation.

Results

Among 4554 patients with PDAC some 987 (21.7%) and 3567 (78.3%) did or did not receive PERT, respectively.

Before matching patients in the PERT group were younger (mean age of 69 vs. 73.2 years, respectively; $p < 0.001$), lived in more deprived areas ($p < 0.001$), diagnosed with PDAC more recently ($p < 0.001$), lower baseline Charlson index (mean Charlson index of 3.74 vs. 4.58; $p < 0.001$), had a higher percentage of patients who had received chemotherapy (45.8% vs. 20.8%; $p < 0.001$), pancreaticoduodenectomy (25.3% vs. 2.1%; $p < 0.001$), total pancreatectomy (2.3% vs. 0.1%; $p < 0.001$), and distal pancreatectomy surgery (2.4% vs. 0.8%; $p < 0.001$) than those in the non-PERT-treated control group. Baseline characteristics are detailed in Table S2.

Trends in treatment are shown in Fig. 1; the proportion of patients receiving PERT increased over time (8.9% in 1998; 34.0% in 2014) as did those receiving chemotherapy (5.5% vs 25.7% respectively) or undergoing surgery (6.2% vs 14.1% respectively). The one year survival increased from 18.6% to 27.7% between 1998 and 2014.

Descriptives (after matching)

A total of 807 PDAC subjects treated with PERT were identified were matched to 807 non-PERT-treated PDAC controls. Subjects were followed from their index date for an average of 371.8 (median 193) days, representing a censored total follow-up period of 1643 years.

There were no major differences in the baseline characteristics of patients between PERT-treated cases and non-PERT-treated controls (Table S2).

In total, there were 1403 deaths, corresponding to an unadjusted event rate of 854 deaths per 1000 person-years.

Unadjusted event rates were highest in the control group and lowest in the PERT group (994 vs. 748 per 1000 person-years, respectively; $p < 0.001$; Table 2). Unadjusted event rates were lowest in people aged <65 years at index date and highest for people aged >75 years for both PERT and control subjects.

Unadjusted survival patterns

Among the whole cohort, 807 patient pairs could be matched (Table S3). Propensity matched analysis demonstrated that the median survival was significantly greater among those patients receiving PERT (274 vs 140 days, $p < 0.001$; Fig. 2a). The exclusion of patients undergoing surgery did not change the significant association of PERT and increased survival (683 patient pairs, 238 vs 119 days, $p < 0.001$, Fig. 2b). The effect of PERT was further analysed among this group of patients with unresectable disease into those patients that did or did not receive chemotherapy. Among those patients treated with chemotherapy (279 patient pairs) the median survival was 328 days and 226 days for those patients receiving PERT or not ($p < 0.0006$; Fig. 2c). Among those patients who did not receive chemotherapy (408 patient pairs) the median survival was 171 days and 71 days for those patients receiving PERT or not ($p < 0.001$, Fig. 2d). One year survival estimates for these groups are provided in Table 1.

Adjusted survival patterns

The full model consisted of 12 predictors, several of which had limited contributions. Predictors that had a relatively large effect were age, smoking status, Charlson index, chemotherapy, pancreaticoduodenectomy surgery, and treatment with PERT or not. We tested interactions between predictors but the resultant interactions were not statistically significant and therefore not included in the final model. The adequacy of model fit was assessed and indicated a reasonable fit to the log logistic model. After stepwise selection the final model was found to be optimal with 6 predictors (Table S4). Predictors with non-significant effects (socioeconomic status, self-assigned ethnicity, gender, index year, total pancreatectomy surgery, and distal or partial resection surgery) were excluded from the reduced model.

Effect size and direction of these 6 model covariates are detailed in Fig. 3. With reference to the observed survival in the cohort of patients with PDAC, the median survival time was 262% greater in PERT-treated cases (STR = 2.62, 95% CI 2.27–3.02) when compared with matched, non-PERT-treated controls (Fig. 3).

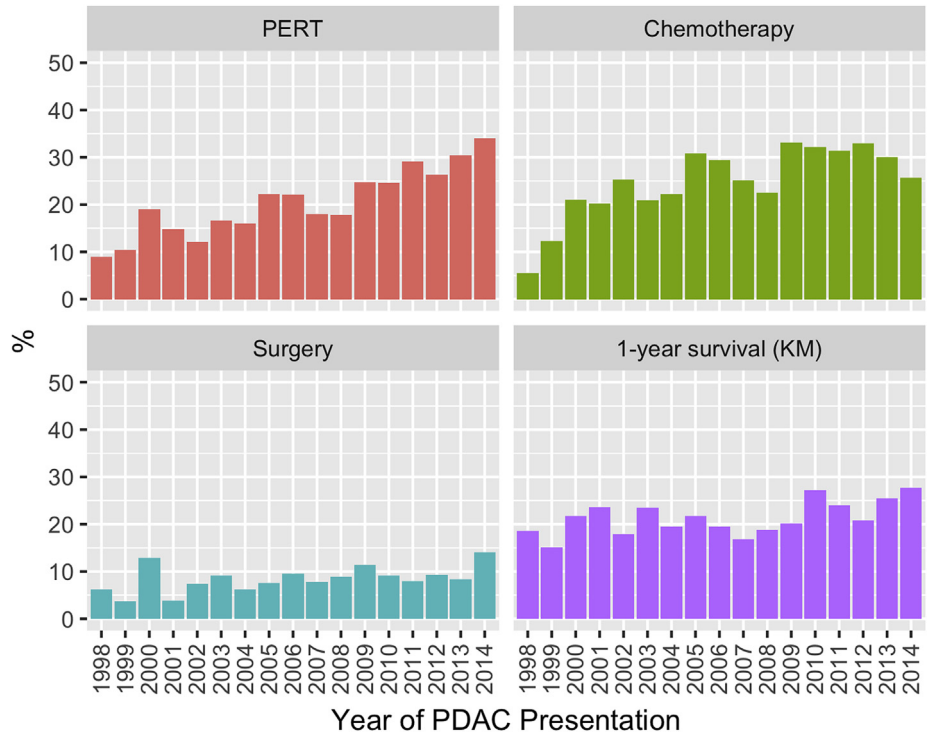

Fig. 1. Proportion of patients that receive PERT, chemotherapy, resectional surgery, and KM estimates of 1-year survival, stratified by year of diagnosis of PDAC.

Table 1
Kaplan–Meier estimates of 1-year survival, comparing PERT-treated PDAC patients with their matched non-PERT treated control group (a) overall, (b) only patients who did not undergo surgery, (c) only patients who did not undergo surgery and received chemotherapy, and (d) only patients who did not undergo surgery but did not receive chemotherapy.

Group	PERT	Controls
(a) Overall	0.39	0.22
(b) Non-surgical subgroup	0.32	0.16
(c) Non-surgical, chemo subgroup	0.43	0.26
(d) Non-surgical, non-chemo subgroup	0.25	0.09

Table 2
Crude event rate per 1000 person-years for all-cause mortality for patients with pancreatic cancer treated with PERT, or their respective matched, non-PERT-treated controls.

	Parameter	PERT	Controls
Overall	Number of deaths	699	704
	Follow-up period (years)	935	708
	Crude event rate	748	994
Age <65 years	Number of deaths	209	248
	Follow-up period (years)	326	344
	Crude event rate	641	721
Age 65–75 years	Number of deaths	260	238
	Follow-up period (years)	348	232
	Crude event rate	747	1026
Age >75 years	Number of deaths	230	218
	Follow-up period (years)	261	132
	Crude event rate	882	1650

These patterns remained generally consistent across a wide range of clinically relevant subgroups (Fig. 4). The central points of the STRs did not cross unity in a discordant way in analysis of any subgroup. Furthermore, the treatment effect of PERT remained significant after excluding patients that died within 30, 60 or 90 days of diagnosis.

Discussion

This population based observational study among patients with PDAC was an analysis of survival between matched patients who did or did not receive PERT. The main finding was that survival was greater among those patients receiving PERT. The magnitude of survival benefit was not trivial, being associated with a 1.96 to 2.59 increase in survival among the matched cohorts (without and with risk adjustment respectively). This observation is remarkable given the modest benefits associated with palliative chemotherapies [5,26]. Subgroup analysis demonstrated that the observed effect of PERT provided a significant survival benefit in a range of clinically relevant subgroups. Furthermore, among patients receiving no chemotherapy or surgery PERT appears to improve survival which demonstrates the benefit is (at least partly) independent of established therapies for PDAC. This is an important observation given over 80% of patients with PDAC have unresectable disease and among these the majority never receive palliative therapy [7]. Whilst it is clear that PERT is not a replacement for established therapy the data of this study demonstrates survival benefit over and above established therapies.

There is existing evidence that malnutrition among patients with PDAC is clinically significant. At diagnosis, the majority of patients have lost weight [27]; the amount of weight loss correlating with reduced survival [16]. Patients are often deficient in fat soluble vitamins and trace elements [14]. Effects of PEI negatively influence quality of life [11].

PERT is physiological, has negligible side effects and relatively low cost, can be delivered by non-specialists in the community and as such should be considered as a standard of care among these patients. Furthermore, untreated PEI negatively impacts quality of life [11] and therefore this treatment is likely to be highly cost effective.

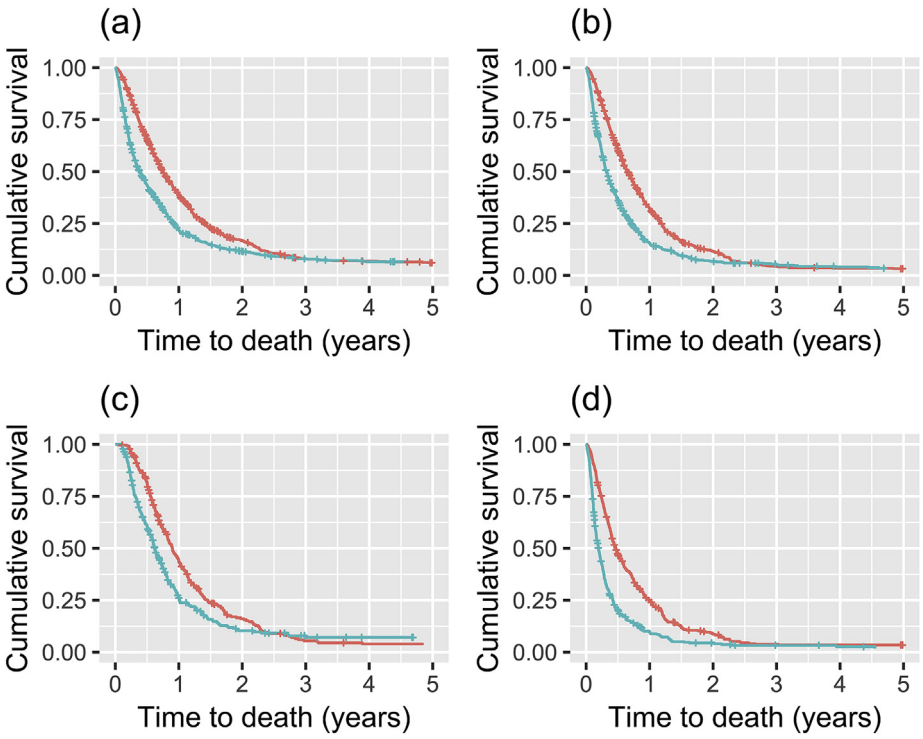

Fig. 2. Kaplan–Meier curves comparing PERT-treated PDAC patients [red line] with their matched non-PERT treated control [green line] group (a) overall, (b) only patients who did not undergo surgery, (c) only patients who did not undergo surgery and received chemotherapy, and (d) only patients who did not undergo surgery but did not receive chemotherapy.

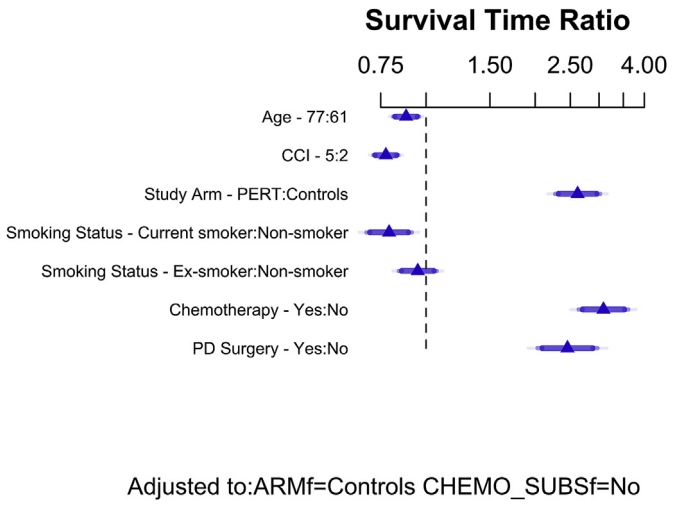

Fig. 3. Estimated survival time ratios for default settings of predictors. For example when age changes from its lower quartile to its upper quartile (61y to 77y), median survival time decrease by 12%. Different shaded areas of bars indicate different confidence levels (0.90, 0.95, 0.99).

The importance of addressing malnutrition and PEI among patients with PDAC is recognised in national and expert practice guidance [28,29]. The low rate of PERT use in this study therefore appears remarkable, however, is not without precedent; a study among European patients following surgery demonstrated the majority of patients with PEI received no or undertreatment [27] whilst a study of patients with metastatic PDAC from Australia demonstrated that just 21% of patients with malabsorption were prescribed PERT [17]. The reasons for under-treatment remain to be defined. There is a lack of high-level evidence base which may help explain why PERT is not used more widely. Two randomised trials, both with small patient numbers, demonstrate differing results. A Dutch study [29] randomised 21 patients with unresectable cancer to placebo or PERT for 8 weeks. Patients receiving placebo lost 3.7% body weight whilst those receiving PERT gained 1.2% body weight over the study period. This was associated with a higher daily intake of calories and protein among the PERT group. Quality of life was not formally assessed though stool frequency showed a non-significant ($p = 0.07$) improvement among patients receiving PERT. A Korean study [30] randomised 67 patients to PERT or placebo though that study demonstrated no significant difference in weight change, patient reported outcomes or overall survival between the groups. However just 34% of patients had tumours in the pancreatic head suggesting the majority of patients had a reasonable proportion of the gland unaffected by pancreatic duct obstruction. A subgroup analysis among those patients with tumours within the pancreatic head demonstrated that there was a significant improvement in patient reported symptoms and global assessment of nutrition associated with PERT use. Furthermore H2-receptor antagonists and proton pump inhibitors were stopped among all patients in that trial to 'reduce variability'. It is possible that the efficacy of PERT was consequently impaired as lipase is released from coated PERT at a pH greater than 5. Under normal circumstances gastric acid is neutralised due to bicarbonate secretion from the pancreas. The addition of a proton pump inhibitor to limit gastric acid production is a viable method to increase the efficacy of PERT [31].

Due to the method of data collection the present study was not able to ascertain the prevalence of PEI among the cohort and thus it is unclear what proportion of the treated or untreated populations had PEI. However, the observed use of PERT in the present study (21.7%) suggests that a large proportion of patients were

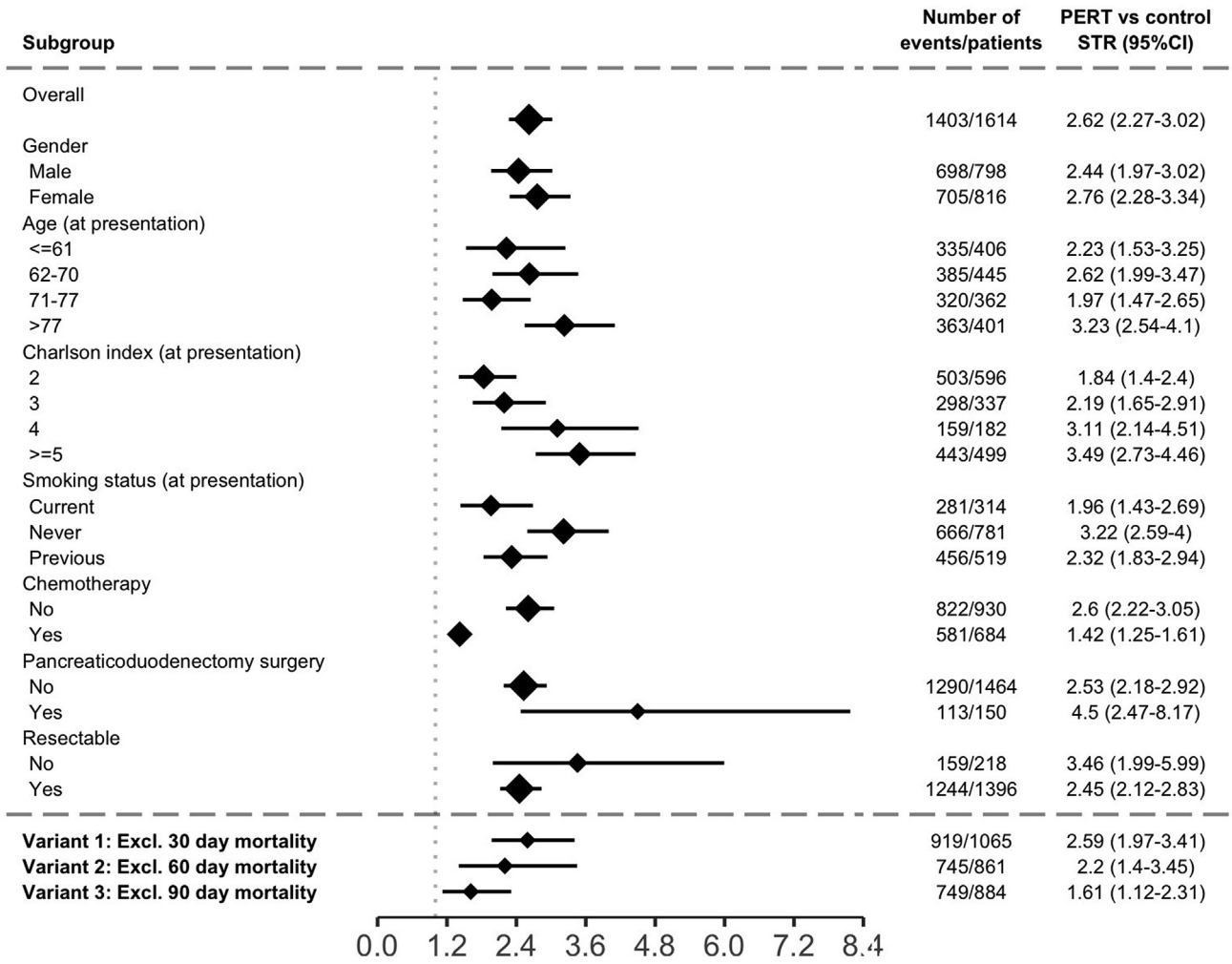

Fig. 4. Forest plot showing adjusted survival time ratios (STR), overall and for relevant subgroups. Data are for PDAC patients initiated with PERT therapy versus non-PERT-treated controls. Final model: Covariates were age, smoking status, Charlson index, chemotherapy, pancreaticoduodenectomy surgery, and study arm. Model variants 1–3: Covariates were the same as the final model, but with 30-, 60-, and 90-day mortality excluded in model variants 1, 2, and 3, respectively.

undertreated given the expected prevalence of PEI among these patient populations [11]. A further unquantified variable in this study is dosage. It was not possible to accurately determine daily dosage for the majority of patients receiving PERT. The optimal dose of PERT remains to be defined; in a recent study there was evidence of a dose effect with a non-significant increase in survival among patients with a higher daily dose of PERT [19]. Among RCT's enzyme doses of 72–75,000 Ph.U. of lipase with meals and 36–50,000 Ph.U. of lipase with snacks improves fat digestion [32]. Smaller doses of PERT were typically used in earlier studies [29]. Given that this study includes patients treated since 2001 it is possible that even among patients receiving PERT, therapy may have been suboptimal.

It is essential to consider why PERT may improve survival. Review of the survival curves demonstrates that it is median and not overall survival that is affected. This likely reflects the fact that untreated PEI will result in weight loss, frailty and an inability to recovery from major surgery, tolerate chemotherapy and to withstand the progression of cancer. It does not appear that PERT improves overall survival in this setting suggesting PERT has no anti-tumour activity which is perhaps unsurprising. However among patients with chronic pancreatitis PERT appears to improve survival among patients who do [18] or do not [33] undergo surgery.

There are clear limitations of this study. Unlike RCTs, less strict inclusion and exclusion criteria are often used in observational studies. The data source used for this study, CPRD, contained data collected from routine practice; therefore, some data may be missing and coding imperfections may lead to PDAC and/or case/control misclassification. However, only those patient records meeting CPRD's quality criteria were included. Data quality in CPRD is considered to be good [34]. As this was an observational study, patients were not randomised to treatment, and uncharacterised confounders may account for some of the differences between groups. Although differences in baseline characteristics existed between the two groups, these were adjusted for as far as possible in the matching and the modelling. However, we could not adjust for some parameters due to the understandably high percentage of missing data. We did not investigate for a dose–response association in this study; however, this would be interesting.

It was not possible to study effects upon patients undergoing surgery in a subgroup analysis due to low numbers of patients though a recent single centre study demonstrated increased survival among a propensity matched cohort of patients undergoing pancreatoduodenectomy for cancer [19]. Using national registries relies upon accurate coding of disease and treatments. The median and overall survival of patients with PDAC in this study is comparable to what one would expect suggesting the patient population

has been accurately identified. There are long term survivors in the cohort not receiving surgery suggesting patient selection is not 100% accurate; however, the numbers of patients is very low (n = 28, 2.01%) and there was no difference between the PERT and no PERT cohorts. The effects of patient and treatment variables such as age, comorbidity, surgery and chemotherapy upon survival are also consistent with expectation. Thus, the association between increased survival and PERT appears reliable. Though access to national registries identified all patients with PDAC and those who received surgery/chemotherapy identification of PERT use could only be applied to a cohort of patients whose general practitioners contribute to the CPRD database. Thus this is not an analysis of the full cross section of England or the UK, however, restricting cohort membership to patients from the subset of English practices participating in the linkage scheme between CPRD and HES/ONS should not have introduced significant bias; patient characteristics have been found to be similar between linked and nonlinked practices [21].

It is debatable whether studies such as this represent the pinnacle of evidence base or whether large randomised controlled trial(s) are needed to confirm the importance of PERT. Given the evidence for PERT it would appear there would be no equipoise within a trial where a control group of patients did not receive PERT. However, this statement contrasts with the observation that the majority of patients with PDAC do not receive PERT despite the apparent benefits and recommendations.

In summary, this population-based study identifies that patients with PDAC who receive PERT benefit from an increased median survival. However, the use of PERT among patients with PDAC appears low. Reasons for this should be identified whilst the optimal dose of PERT remains to be defined.

Conflict of interests of authors

KR and HS are independent clinicians but were paid consultancy fees by Mylan Pharmaceuticals to undertake this study. Digital Health Labs were funded directly to obtain the data and perform the statistical analysis (CB is an employee of Digital Health Labs). No author is a member of staff of Mylan Pharmaceuticals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2018.10.010

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