Review Article

Selected pre-operative factors which affect pancreaticoduodenectomy outcomes: a systematic review

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Background: Pancreatic ductal adenocarcinoma (PDAC) affecting the head of the pancreas carries a dismal prognosis. For those with early disease, pancreaticoduodenectomy (PD) remains the only curative-intent treatment option. This is associated with considerable peri-operative morbidity and most patients develop disease recurrence. A greater understanding of the pre-operative factors which affect PD outcomes will improve patient selection, guide risk/benefit discussions and allow for pre-operative patient optimisation. We aimed to consolidate the recent literature on selected pre-operative factors and their impact on PD outcomes. The factors selected are currently being investigated by the Recurrence After Whipple's (RAW) study.

Methods: A systematic search of the English literature (PubMed database) was carried out. Articles from May 2011 to May 2021 reporting on clinical studies with outcomes on PD for PDAC were included.

Results: One thousand, nine hundred and thirteen records were identified. Ninety-six were included in the final synthesis. Advanced age, as well as pre-existing cardiac and/or respiratory disease all increase peri-operative morbidity/mortality, but the impact of diabetes mellitus (DM) is less clear. Unhealthy body mass index (BMI) is associated with worse short-term outcomes and evidence is emerging which suggests sarcopenia and myosteatosis may affect short- and long-term outcomes. The impact of pre-operative biliary stenting (PBS) remains controversial and numerous laboratory/imaging findings can predict survival.

Discussion: Many of the factors investigated are non-modifiable. An appreciation for these allows clinicians to make an informed assessment of potential surgical candidates and can guide discussions surrounding risk and benefit. Important non-modifiable risk factors include advanced age and various laboratory/imaging findings. In this context, obesity can also be considered non-modifiable since obese patients are unlikely to significantly alter their body habitus prior to PD. Other factors, such as pre-existing cardiac disease, respiratory disease, and diabetes, are modifiable. Optimisation of these may reduce morbidity and increase the proportion of patients who complete adjuvant chemotherapy. The influence of many of the factors discussed are limited to single-centre retrospective analyses and may not include all confounding variables. Hence, a rigorous study is required.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); pancreatic cancer; pancreaticoduodenectomy (PD); morbidity; survival

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fifth biggest cancer killer in the United Kingdom (UK); five-year survival is around 7% (1). For patients with early disease affecting the head of the pancreas, the only treatment option which provides the possibility of long-term survival is surgical resection in the form of pancreaticoduodenectomy (PD). Despite improvements to surgical technique, patient selection and peri-operative care, morbidity remains high and most patients develop recurrent disease. This review aims to consolidate the recent literature on pre-selected pre-operative factors which affect peri-operative and survival outcomes following PD performed for suspected PDAC. The factors selected are currently being investigated by the Recurrence After Whipple's (RAW) study (https://clinicaltrials.gov/ct2/show/NCT04596865). An appreciation of these will guide patient selection, pre-operative optimisation, and risk/benefit discussions with potential surgical candidates. Data on these factors will also allow for the development of predictive models so that the likelihood of certain outcomes can be estimated in individual patients. We present the following article in accordance with the PRISMA checklist (available at https://dx.doi.org/10.21037/apc-21-15).

Methods

The pre-operative factors included were all selected prior to carrying out the literature search. These were: age, gender, body mass index (BMI), sarcopenia, myosteatosis, diabetes mellitus (DM), cardiac disease, respiratory disease, radiological tumour characteristics, neoadjuvant treatment (NAT), biliary stenting, bilirubin, C-reactive protein (CRP), albumin, C-reactive protein/albumin ratio (CAR) and neutrophil/lymphocyte ratio (NLR). A systematic search of the English literature was carried out on 1st June 2021. The PubMed database were searched using the terms "pre-operative factor in question", "pancreaticoduodenectomy", and "outcome" from May 2011 through May 2021. The following articles were included: (I) human studies; (II) English language; (III) meta-analyses (MA), systematic reviews (SR) or clinical studies reporting on peri-operative outcomes and survival following open PD performed for suspected PDAC; (IV) excluding the radiology and NAT sections, minimum of 100 PDs (if final histological diagnosis specified, at least 100 PDs performed for PDAC); (V) in terms of risk factors/associations, only statistically significant results were included (P<0.05); (VI) to reduce the impact of bias, studies were only included if the "pre-operative factor in question" was investigated as a primary outcome measure and did not depend on other factors. For the radiological features section, a non-systematic search was undertaken (not using the stated criteria) to identify articles reporting on specific radiological features which affect PD outcomes. Concerning NAT, only articles reporting on comparisons between NAT and standard of care (upfront surgery) were included, and those comparing different NAT regimens were excluded. For the biliary stenting section, only studies comparing stenting to upfront surgery were included, and studies comparing stenting methods or timing of PBS were excluded.

The initial search returned 1,913 records (*Figure 1*). After initial screening, 1,711 articles were excluded as they did not meet the inclusion criteria. Following an in-depth review of the remaining articles, a further 106 were excluded. Ninety-six articles were included in the final analysis. Eleven of these were SRs/MAs and the remainder were single/multi-centre studies. *Figure 1* illustrates the breakdown. No amendments were made to the original methods.

Results

Age

Median age at PDAC diagnosis is 70 years and the average age of patients presenting with resectable disease is set to rise (2). Whilst decisions to operate must never be based solely on numerical age, a pragmatic and patient-centred approach should be employed. Multiple recent studies have concluded that it is safe and reasonable to perform PD in selected older patients. Shamali *et al.* (3) (n=524) showed that patients aged ≥75 years had similar rates of overall morbidity and major morbidity compared to younger patients. Furthermore, age was not an independent predictor of five-year or overall survival (OS) (3). However, the older patients were more likely to experience cardiac complications (10.8% *vs.* 3.6%, P=0.008) and had higher peri-operative mortality (5.9% *vs.* 1.9%, P=0.037). In contrast, El Nakeeb *et al.* (4) (n=828) found patients aged >70 years had the highest overall morbidity, followed by those aged 60–70 years, followed by under 60s (25.9% *vs.* 36.8% *vs.* 37.5%, P=0.006). However, peri-operative mortality rates were similar (4). Zhang *et al.* (5) (n=216) reached similar conclusions. Patients >70 years had similar

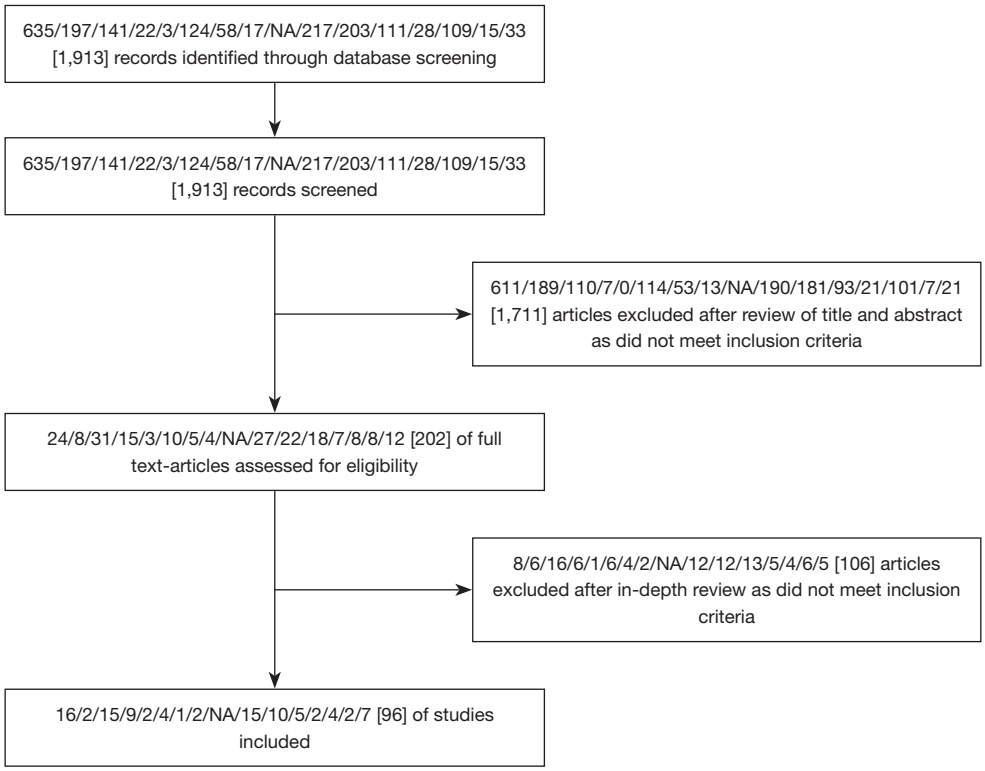

Figure 1 Flow of information diagram. Numbers represent total number of articles on age/gender/BMI/sarcopenia/myosteatosis/diabetes/cardiac disease/respiratory disease/radiological staging/NAT/biliary stenting/bilirubin/CRP/albumin/CAR/NLR [total number of studies]. Eleven systematic reviews/meta-analysis were included (age: one; BMI: one; diabetes: two; neaoadjuvant therapy: three; PBS: two; CRP: one; NLR: one). The remaining studies were single/multi-centre clinical studies. Risk of bias assessment was not performed for each individual study. Effect estimates and precision figures are quoted in the main text. BMI, body mass index; NAT, neoadjuvant treatment; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio; NLR, neutrophil/lymphocyte ratio; PBS, pre-operative biliary stenting.

morbidity and mortality rates to those ≤70, but were more likely to experience cardiac (P=0.008) or respiratory (P=0.013) complications, and had longer length of stay (P=0.013). Similarly, Wiltberger *et al.* (6) (n=370) found that age did not affect overall mortality, but that increasing age was associated with major morbidity (P<0.05).

Gruppo *et al.* (7) (n=106) found that being aged >70 years did not affect overall morbidity, peri-operative mortality, or OS. Other authors have reached similar conclusions using thresholds of 75 (8-10) and 80 years (2,11). In contrast, Oguro *et al.* (12) (n=561, 13 *vs.* 82 months, P=0.014) and Kim *et al.* (13) (n=165, 16.6 *vs.* 22.5 months, P=0.048) found OS was shorter in those aged >80 years.

The studies discussed will have been influenced by selection bias as older patients will have been pre-assessed as suitable surgical candidates based on their performance status and pre-existing co-morbidities. Hence, the effect of increasing age is likely underestimated. A recent SR by Kim *et al.* (14) (18 studies, n=49,449) concluded that over 80s have a 50% increased risk of peri-operative morbidity and a 100% increased risk of peri-operative mortality compared to under 80s. Haigh *et al.* (15) (n=2,610), also found that over 70s had higher rates of morbidity (40.7% *vs.* 34.0%, P=0.01) and mortality (4.7% *vs.* 1.3%, P=0.01). Further authors have reached similar conclusions using thresholds of 75 (16) and 80 years (17). As such, careful patient selection is required when deciding to operate on the elderly, but advanced age alone is not an absolute contraindication to PD.

Gender

No recent studies have specifically compared outcomes in males and females. Williamsson *et al.* (18) investigated for gender differences in treatment and outcomes following a

diagnosis of a pancreatic head malignancy. All patients in the Swedish national database (2012–2017) were included (n=5,677, 4,227 of which had pancreatic cancer). Females were significantly older than males at time of diagnosis (72 *vs.* 70 years, P<0.001) and a lower proportion underwent curative-intent surgery (41 *vs.* 44, P=0.008). However, once age and tumour location were adjusted for, no difference was observed (18). Females had shorter operation times (376 *vs.* 402 min, P<0.001) and reduced intra-operative blood loss (400 *vs.* 600 mL, P<0.001), which may be because men tend to have a higher proportion of intra-abdominal fat (18). No difference in overall morbidity, length of stay or peri-operative mortality was observed (18). Five-year survival following resection was significantly higher in females (8.1% *vs.* 5.7%, P=0.046) (18). Hence, the authors concluded that it may be reasonable to offer females PD at a more advanced age (18).

Mazmudar *et al.* (19) (n=22,086) found, after adjusting for confounding factors, males were more likely to have an operation lasting more than 6 h (28.0% *vs.* 18.3%), and had higher intra-operative blood transfusion rates (14.4% *vs.* 14.0%), higher surgical site infection (SSI) rates (20.4% *vs.* 17.1%) and longer length of stay (9.4 *vs.* 9.1 days, all P<0.001). Again, the authors suggested that this may be the result of higher rates of abdominal-type obesity among males (19). Male sex was not associated with increased peri-operative mortality, and long-term outcomes were not studied (19).

BMI

Numerous studies have concluded that patients of an unhealthy weight are at increased risk of morbidity. The threshold BMI used varies considerably between studies. Chen *et al.* (20) (n=362) concluded that BMI >24 kg/m^2 was associated with increased morbidity (42.9% *vs.* 29.6%, P=0.009), but not mortality. Aoki *et al.* (21) found that BMI >25 kg/m^2 was a risk factor for grade C postoperative pancreatic fistula (POPF; OR =1.8) and major morbidity (OR =1.84; both P<0.001). Tang *et al.* (22) (n=227) reached similar conclusions. El Nakeeb *et al.* (23) (n=471) found that BMI >25 kg/m^2 was associated with longer operation times (5.35 *vs.* 5.0 h, P=0.003), POPF (25.0% *vs.* 8.1%, P<0.001), overall morbidity (33.0% *vs.* 17.3%, P=0.001) and peri-operative mortality (7.1% *vs.* 0.8%, P=0.001). Del Chiaro *et al.* (24) (n=367) also found BMI >25 kg/m^2 was associated with increased intra-operative blood loss (1,392 *vs.* 1,121 mL, P=0.01) and risk of POPF (20.0% *vs.* 9.5%, P=0.006), and Greenblatt *et al.* (25) (n=4,945) concluded that BMI >25 kg/m^2 was a predictor of overall morbidity (P<0.05), but not peri-operative mortality. A recent SR and MA by You *et al.* (26) (22 studies, n=8,994) compared high BMI (>25 kg/m^2) to low BMI (<25 kg/m^2). High BMI was associated with increased operation time (mean increase: 15 min), increased intra-operative blood loss (mean difference: 271 mL), POPF (OR =1.96), delayed gastric emptying (DGE; OR =1.62), SSI (OR =1.43), and longer length of stay (mean difference: 2.87 days; all P<0.05) (26).

Using a threshold BMI of 30 kg/m^2, Wiltberger *et al.* (6) (n=405) concluded that obese patients were more likely to experience major morbidity (P=0.05). Similarly, Ekström *et al.* (27) (n=328) found that obesity was associated with increased major morbidity (OR =1.72; P=0.001) and grade B/C POPF (OR =4.16; P=0.001). Using the same threshold, Chang *et al.* (28) (n=3,484), concluded that obesity was associated with increased rates of SSI (OR =1.38; P=0.01), unplanned return to theatre (OR =1.39; P<0.05), failure to extubate after 48 h (OR =1.6; P=0.02), septic shock (OR =2.2; P=0.0002), and peri-operative mortality (OR =1.7; P<0.05).

Zorbas *et al.* (29) (n=2,667), found that severe (or morbid) obesity (BMI ≥40 kg/m^2) was a risk factor for pulmonary embolism (2.2% *vs.* 0.9%, P=0.048), POPF (30.4% *vs.* 16.1%, P<0.0005), SSI (15.2% *vs.* 8.9%, P<0.0005), renal failure (3.3% *vs.* 0.4%, P=0.003), and overall morbidity (65.2% *vs.* 47.8%, P<0.001), but not peri-operative mortality.

The increased risks associated with obesity are well documented but being underweight also has associated risks. Pausch *et al.* (30) (n=408) found that patients with BMI <18.5 kg/m^2 had higher peri-operative mortality (P<0.048). However, this included just 16 patients in the underweight category and these findings have not been validated by larger studies. It is likely that it is malnutrition and cachexia, rather than low BMI alone, which contributes to adverse outcome.

Whilst many studies have investigated the impact of BMI on short-term outcomes, few have considered long-term outcomes. Tsai *et al.* (31) (n=795) concluded that overweight (BMI ≥25 kg/m^2) and obese (BMI ≥30 kg/m^2) patients had improved five-year survival versus normal weight patients (22% *vs.* 22% *vs.* 15%, P=0.02). Two similar studies did not observe this (32,33).

Sarcopenia

Sarcopenia is a syndrome which results in the progressive

loss of skeletal muscle quality and mass, and a low level of physical performance; definitions vary between sources (34). Sarcopenia can be evaluated by assessing psoas mass and density on abdominal computed tomography (CT) at the level of the third lumbar vertebra (35). Numerous recent studies have investigated the impact of CT changes associated with sarcopenia on PD outcomes. Linder *et al.* (36) (n=139) found an association between pre-operative sarcopenia and severe POPF (OR =4.3; P=0.03). Several other authors have arrived at the same conclusion (37-40). Takagi *et al.* (41) (n=219) showed sarcopenic patients had higher rates of infective complications (67.2% *vs.* 40.2%, P<0.001) and peri-operative mortality (5.5% *vs.* 0.0%, P=0.004).

Concerning long-term outcomes, Ryu *et al.* (40) (n=252) found that pre-operative sarcopenia was associated with decreased five-year survival (23.4% *vs.* 28.4%, P=0.046). An association was also demonstrated between sarcopenic obesity and POPF (P=0.018) (40). Stretch *et al.* (42) (n=123) also found that sarcopenic patients had reduced OS (16.0 *vs.* 26.4 months, P=0.005). Peng *et al.* (43) (n=116) and Gruber *et al.* (44) (n=133) reached similar conclusions. The latter also showed that patients with sarcopenic obesity had even worse OS (14 *vs.* 23 months, P=0.007) and higher major morbidity rates (13.5% *vs.* 1.5%, P<0.001) than sarcopenic patients of a healthy weight (44).

Myosteatosis

Myosteatosis refers to fat deposition within the muscles; it can be assessed using CT or magnetic resonance imaging (MRI) where it appears as low skeletal muscle radiation attenuation. Although few studies have investigated the impact of myosteatosis on long-term outcomes of PD, Stretch *et al.* (42) (n=123) concluded that myosteatosis was associated with reduced OS, but only when in combination with sarcopenia (P=0.002). Only a trend was observed in myosteatosis patients without sarcopenia (P=0.06). Similarly, few studies have investigated the impact of pre-operative myosteatosis on peri-operative outcomes. However, there is recent evidence to suggest an association with increased morbidity following resection for oesophageal and gastric cancers (45). West *et al.* (46) (n=123) prospectively studied patients undergoing hepatobiliary and pancreatic surgery (all resections) and found that myosteatosis on pre-operative CT was associated with worse pre-operative fitness as measured by cardiopulmonary exercise testing (CPET) (P<0.001). The authors concluded that combining myosteatosis and physical fitness variables may be useful for stratifying risk (46). One would expect patients with myosteatosis to have worse peri-operative outcomes, but this remains unproven. Furthermore, it is unknown if optimising patients with myosteatosis would be of benefit.

DM

The impact of DM on outcomes following PD remains controversial. Lv *et al.* (47) carried out a MA (17 observational studies, n=5,407 patients, all forms of pancreatic resection included) and found that diabetic patients had higher prevalence of male sex (P=0.01) and higher BMI (P<0.001). No differences were observed in age, smoking status, prevalence of jaundice, operation time, or rate of intra-operative blood transfusion (47). Histologically, DM patients were more likely to have poorly differentiated (P=0.03), larger tumours (P<0.001), and "hard" pancreas consistency (P<0.001) (47). Cancer stage and margin status were comparable between the two groups (47). The authors, like Nakata *et al.* (48) in another SR, did not find DM affected overall morbidity or perioperative mortality (47,48).

POPF is a significant and well-documented complication of pancreatic resection which has been associated with DM since diabetics are thought to have a softer pancreas due to higher fat content. Small calibre pancreatic duct and soft pancreas consistency are known predisposing factors. Lv *et al.* (47) and Xia *et al.* (49) (MA of 16 studies) found similar prevalence of small pancreatic duct and soft pancreas consistency among diabetics and non-diabetics. No association between DM and POPF was observed (47,49). This may be accounted for by patient selection and the high levels of attention which are often given to high-risk patients. Another complication often linked with DM is DGE. In contrast to a few small case series, no large studies have suggested that diabetics are at increased risk of DGE.

Long-term hyperglycaemia is known to impair immune function. Hence, DM is often presumed to increase the risk of infective complications. King *et al.* (50) concluded that poorly controlled diabetics are more likely to experience infective complications when undergoing general and vascular surgery. Whilst the underlying mechanisms are not well understood, it is thought hyperglycaemia can affect chemotaxis, the activation of macrophages, pathogen opsonisation, and phagocytosis (51). However, the MA by Lv *et al.* did not identify DM as a predictor of infective complications (47). This study did show that a recent diagnosis of DM (within two years of resection) was associated with reduced OS following PD (RR =1.35;

P<0.001) (47).

Cardiac disease

The impact of acute and chronic cardiac disease on pancreatic resection outcomes was investigated by Ronnekleiv-Kelly *et al.* (52) in a large retrospective cohort study using USA national data (n=13,021, 2/3 underwent PD). Patients were categorised as having a history of cardiac disease if they had a prior diagnosis of congestive cardiac failure (CCF), angina, or myocardial infarction (MI), or if they had any history of percutaneous coronary intervention or cardiac surgery. Eleven percent of patients had pre-existing cardiac disease and a 1.1% sub-set had "acute cardiac disease" (defined as CCF symptoms within 30 days, angina within 1 month, or MI within 6 months of surgery). Those with cardiac disease were older, more co-morbid, more likely to be male, and were more likely to experience cardiac complications (all P<0.001). Patients with acute cardiac disease were at even higher risk of cardiac complications (P<0.001) (52). A history of cardiac disease and acute cardiac disease were associated with a 1.6- (P<0.0001) and 1.8-fold (P<0.0007) increase in major morbidity, and a 2.3- (P<0.0001) and 4.2-fold (P<0.0001) increase in peri-operative mortality, respectively (52). Other studies which did not specifically investigate the impact of pre-existing cardiac disease have come to similar conclusions (25,53,54). It is unknown whether pre-existing cardiac disease affects long-term PD outcomes.

Respiratory disease

It is important to identify patients with pre-existing respiratory disease and optimise their functional status wherever possible. It is also important that patients are risk-stratified and that, as with cardiac disease, their increased level of risk is discussed with them. Pre-operative CPET can provide estimates of aerobic and anaerobic threshold to aid in pre-operative planning for the peri-operative period. Few large studies have specifically investigated the impact of pre-operative respiratory co-morbidities on PD outcomes. This is likely because those with significant respiratory disease are unlikely to be considered surgical candidates. Shia *et al.* (55) (n=8,490) found pre-existing chronic obstructive pulmonary disease independently reduced 90-day survival (aHR =1.35; P<0.001) and Aoki *et al.* (21) (n=17,564) found those with pre-existing respiratory co-morbidities had higher major morbidity (OR =1.86; P=0.012) and grade C POPF (OR =2.08; P=0.0002) rates.

Radiological features

To our knowledge, no studies have specifically investigated the impact of radiological stage on PD outcomes. One would assume that more advanced stage is associated with worse short- and long-term outcomes. Several recent studies have attempted to identify radiologic features as prognostic predictors. Lee *et al.* (56) (n=143) studied patients who underwent MRI within one month of PD and were subsequently found to have an R0 resection. Rim-enhancement at dynamic contrast material-enhanced MRI was associated with reduced three-year DFS (8.0% *vs.* 24.3%, P=0.008) and three-year OS (19.7% *vs.* 41.0%, P=0.001). Rim-enhancing lesions were also associated with more aggressive tumours on pathologic staging (P=0.002) (56). Several studies have investigated CT tumour characteristics. Kim *et al.* (57) (n=116) found tumours with a heterogeneous texture were associated with reduced DFS (6.72 *vs.* 10.52 months, P=0.025) and Zhu *et al.* (58) (n=79) that lower relative enhancement change was associated with shorter DFS (10.7 *vs.* 17.9 months, P=0.01) and three-year OS (20.3 *vs.* 28.5 months, P=0.01). Cassinotto *et al.* (59) (n=99) studied the portal venous phase of pre-operative scans and concluded that hypoattenuating tumours were associated with reduced one-year DFS (35.0% *vs.* 68.0%, P=0.04).

Positron emission tomography (PET)-CT is a further imaging modality which has been studied. Choi *et al.* (60) (n=64) found patients with a tumour with a maximum standardised uptake value >3.5 had reduced DFS (9.2 *vs.* 26.1 months, P=0.002) and OS (23.5 *vs.* 45.4 months, P=0.002). Yamamoto *et al.* (61), who performed a similar study but used a cut-off value of 6.0, came to the same conclusion. Lee *et al.* (62) (n=87) identified both metabolic tumour volume and total lesion glycolysis as independent predictors of DFS (HR =2.34, P=0.001; HR =2.59, P=0.003) and OS (HR =3.69, P=0.02; HR =4.85, P=0.003).

NAT

NAT aims to treat micrometastases, downstage primary tumours, and increase the chance of patients completing a course of treatment. Currently, UK national guidelines only advise NAT in PDAC patients as part of a clinical trial (63). The use of neoadjuvant chemotherapy (NAC) for resectable/borderline resectable PDAC remains a source of debate and has been the subject of several recent trials. The two-

arm randomised phase II/III Prep02/JSAP05 trial involved 57 Japanese centres. One arm received gemcitabine and S-1 prior to surgery, and the other had upfront surgery. All patients with resectable or borderline resectable PDAC who could tolerate curative-intent surgery were included (n=362). OS was significantly longer in the NAC arm (36.7 *vs.* 26.6 months, P=0.015) (64). No difference was observed in terms of resection rate, R0 resection rate, and overall morbidity (64). The international phase II ESPAC-5F trial contained four arms. This aimed to compare resection rates in those who underwent upfront surgery to gemcitabine/capecitabine NAC, FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin-based) NAC, and neoadjuvant chemo-radiotherapy (NACRT) (n=90). Resection rate was slightly higher in the upfront surgery group, but this was not significant (65). Upfront surgery was associated with reduced one-year survival compared to all NAT arms (40% *vs.* 77%, P<0.001); the authors concluded that NAT should be considered in those with borderline resectable PDAC (65).

The phase III PREOPANC trial involved 16 Dutch centres and aimed to compare outcomes in those who received NACRT to those who received conventional treatment (upfront surgery followed by gemcitabine-based adjuvant chemotherapy) (n=248). All surgical candidates with pathologically confirmed PDAC with resectable or borderline resectable disease were included. T1 tumours were excluded, and randomisation took place prior to biliary drainage. Those in the NACRT arm had a slight survival benefit although this was not significant (66). When those in the NACRT group who failed to progress to surgery were excluded, R0 resection rate was significantly higher in the NACRT group compared to the upfront surgery group (71% *vs.* 40%, P<0.001). Hence, NACRT likely improved the process of selecting surgical candidates (66). When only those who underwent resection and subsequently started adjuvant therapy were included, NACRT provided a further survival benefit (35.2 *vs.* 19.8 months, P=0.029) (66).

A recent MA by Rangarajan *et al.* (67) included 27 studies: three randomised controlled trials (RCTs) and 24 retrospective cohort studies (n=63,151). Improved survival outcomes (HR =0.72; P<0.001), reduced morbidity rates (RR =0.81; P=0.001) and improved R0 resection rates (RR =0.51; P<0.001) were observed in those who received NAC. Greco *et al.* (68) (n=8,472) reached similar conclusions. These studies will have been affected by selection bias since patients who received NAC but failed to progress to surgery were excluded. Both authors concluded that, whilst there may not be strong evidence for NAC in resectable disease, it does confer a survival benefit for select patients and that randomised trials are needed (67). In a further MA by Lee *et al.* (69) (14 studies, n=9,691), NAC was not found to provide a survival benefit. However, patients who received NAC showed improved OS when compared with patients who had upfront surgery and then completed adjuvant treatment (HR =0.82; P<0.001) (69). The authors concluded that, whilst NAC may not provide an obvious survival benefit for all patients, it may have a role in selecting suitable candidates for resection (69).

Whilst the survival benefits of NAT continue to be investigated, it is important to consider whether NAT affects peri-operative outcomes. Kamarajah *et al.* (70) (n=7,975) found that patients receiving NAT had lower rates of unplanned readmission (5.5% *vs.* 7.4%, P=0.006) and that NAT had no effect on length of stay or peri-operative mortality. Cho *et al.* (71) (n=4,416) found patients who received NAT had longer operation times (423 *vs.* 368 min, P<0.001) and were more likely to undergo vascular reconstruction (20.5% *vs.* 8.4%, P<0.001). This is likely because patients who underwent NAT were more likely to have named vessel involvement as their indication for chemotherapy. No difference was observed in morbidity or mortality rates, and those in the NAT group had shorter length of stay (9 *vs.* 10 days, P=0.005) (71). In a similar study, Cools *et al.* (72) (n=3,748) found NAT patients were more likely to undergo named vein resection (35.8% *vs.* 17.6%, P<0.001) and had longer operation times (413 *vs.* 364 min, P<0.001) but were less likely to develop grade C POPF (0.2% *vs.* 1.2%, P<0.001), and had shorter length of stay (9.7 *vs.* 10.9 days, P<0.001). No difference in overall morbidity or peri-operative mortality was observed (72). Youngwirth *et al.* (73) (n=18,243) reached similar conclusions. In contrast, Aziz *et al.* (74) (n=1,445) found that NAT patients were more likely to have unplanned readmissions (18.0% *vs.* 12.2%, P=0.02) and return to theatre (2.1% *vs.* 1.1%, P=0.03), but no difference in peri-operative mortality was observed. The authors acknowledge that these differences may be due to more advanced disease in the NAT group (74). Teng *et al.* (75) (n=5,025) found that NAT was associated with longer operation times, increased transfusion requirement and higher rates of vascular reconstruction and SSI (all P<0.05). However, peri-operative mortality and major morbidity were not affected by NAT.

A recent MA by Kamarajah *et al.* (76) (n=19,416, 19 studies) found NAT was associated with reduced rates of overall POPF (OR =0.57; P<0.001) and grade B/C POPF

(OR =0.55; P<0.001). Mangieri *et al.* (n=10,665) (77) and Marchegiani *et al.* (78) (n=455) reached the same conclusion. The latter also found that NAT was associated with reduced risk of PPH (9.1% *vs.* 14.6%, P=0.02) but increased risk of DGE (11.5% *vs.* 2.9%, P=0.03).

In summary, the use of NAT in the management of PDAC remains controversial. Evidence if emerging which suggests NAT offers a survival benefit and may be useful for identifying appropriate PD candidates. There is also evidence which suggests NAT is associated with reduced length of stay, as well as overall morbidity, POPF and PPH rates. NAT may increase DGE rates and is associated with increased rates of venous resection although this likely reflects pre-operative disease stage. Whether NAT affects unplanned readmission rate remains controversial.

Biliary stenting

This topic is well studied but remains controversial. UK national guidelines advise against routine pre-operative biliary stenting (PBS) prior to PD as the associated risks are thought to outweigh the potential benefits (63). Gong *et al.* (79) recently carried out a MA (27 studies, n=10,445) and found PBS was associated with increased overall morbidity (OR =1.22; P=0.01), DGE (OR =1.21; P=0.02) and SSI (OR =2.06; P<0.0001), but there was no difference in overall mortality or major morbidity. The authors concluded that patients awaiting PD should not undergo PBS unless they have cholangitis or organ failure secondary to an obstructed biliary system (79). In those who did undergo PBS, there was no difference in morbidity between those who underwent endoscopic drainage and those who underwent percutaneous drainage (79). In another recent MA, Scheufele *et al.* (80) (25 studies, n=6,214) found that PBS was associated with increased overall morbidity (OR =1.4; P<0.002).

Numerous single/multi-centre studies have investigated the impact of PBS on PD outcomes. Morris-Stiff *et al.* (81) (n=280) found stenting did not significantly alter pre-operative serum bilirubin, and that stented patients had higher overall morbidity (54% *vs.* 41%, P=0.03), and rates of POPF (26% *vs.* 18%, P=0.03) and intra-abdominal haemorrhage (12.7% *vs.* 5.6%, P=0.03). Hamidi *et al.* (82), who excluded NAT patients, matched 927 PD patients with obstructive jaundice who underwent PBS to 927 who did not. No significant difference in short-term outcomes was observed between the two groups. The authors concluded that PBS is safe in those with obstructive jaundice and that it does not need to be avoided (82). De Pastena *et al.* (n=1,500) found that major morbidity and mortality rates were not affected by PBS but did argue that jaundiced patients with a serum bilirubin >7.5 mg/dL should be considered for PBS.

El Nakeeb *et al.* (83) (n=588) found that PBS was associated with higher overall morbidity (32.5% *vs.* 24.1%, P=0.03), and higher risk of POPF (18.8% *vs.* 9.8%, P=0.002) and bile leak (10.5% *vs.* 5.8%, P=0.04). Mean length of stay was also longer in the drainage group (10 *vs.* 8 days, P=0.01). Sahora *et al.* (84) (n=1,000) showed that SSI rates were higher in stented patients (19% *vs.* 9%, P=0.001) but PBS did not affect overall morbidity or mortality. In contrast, Bolm *et al.* (85) matched 480 patients who underwent PBS to 480 who underwent upfront surgery (jaundiced and non-jaundiced patients were included) and found PBS was associated with increased major morbidity (27% *vs.* 22%, P=0.027). However, this was not significant in PBS patients who presented with jaundice. Gavazzi *et al.* (86) (n=180) found PBS was associated with deep SSI (13.6% *vs.* 4.4%, P=0.038) but not superficial SSI. Bhatti *et al.* (87) (n=133) found that patients undergoing PBS were more likely to develop SSI (22.7% *vs.* 7.4%, P=0.01) or be re-admitted (10.6% *vs.* 0%, P=0.006), but that PBS did not affect rates of overall peri-operative mortality or grade B/C POPF.

In summary, PBS appears to be associated with higher rates of overall morbidity, DGE, SSI, POPF, bile leak and unplanned readmission. Stented patients may also have longer length of stay. Most authors argue that patients should only undergo PBS if there is a clear indication e.g., cholangitis or organ failure secondary to jaundice. It is important to consider that patients who undergo PBS may be in a worse pre-morbid state than those who undergo upfront surgery and these patients may have higher morbidity rates regardless of their management. It is unknown whether PBS affects long-term PD outcomes.

Pre-operative blood tests

Bilirubin

Multiple prior studies have investigated the impact of serum bilirubin levels on PD outcomes. Scheufele *et al.* (88) (n=304) found that pre-operative bilirubin did not affect overall morbidity or long-term survival. Pamecha *et al.* (89) (n=177) reached similar conclusions but found severe jaundice (≥15 mg/dL) was associated with increased intra-operative blood loss (650 *vs.* 300 mL, P<0.001). Wang *et al.* (90) also reached similar conclusions but found severe jaundice was associated with increased infective complications (56.6%

vs. 36.06%, P<0.05). Dolejs *et al.* (91) (n=2,556) found that pre-operative bilirubin level did not affect overall morbidity, major morbidity, or peri-operative mortality. Yoon *et al.* (92) (n=164) found that pre-operative bilirubin was more likely to be ≥7 mg/dL in those who did not survive 60-months (43.5% *vs.* 5.3%, P=0.01). In summary, whether pre-operative serum bilirubin affects short- and/or long-term PD outcomes remains controversial.

CRP

Pre-operative CRP levels are inversely proportional to survival in a number of cancers. Stevens *et al.* (93) carried out a SR to investigate the role of pre-operative CRP as a prognostic predictor in PDAC patients (n=485). Of the 6 studies which investigated the effect of high CRP on OS, whilst the cut-off value for high CRP varied, 4 suggested a correlation between high CRP and decreased OS. On multivariate analysis, 3 studies observed this finding. The authors concluded that there was insufficient evidence to justify the use of CRP level in clinical decision making. A more recent study by Mansukhani *et al.* (94) (n=133), where CRP levels were taken 48-h prior to surgery, found that CRP was a predictor of infective complications (P<0.01). However, this did not remain significant following multivariate analysis. In summary, high pre-operative CRP may correlate with reduced OS but this does not appear to significantly affect peri-operative outcomes.

Albumin

Serum albumin level is often used as a crude indicator of nutritional status and hepatic synthetic function. Low levels are associated with poor surgical outcomes (95). Rungsakulkij *et al.* (95) (n=238) found low pre-operative serum albumin was a risk factor for major morbidity (OR =0.943; P<0.05). Other studies have also found this (96,97). Hendifar *et al.* (98) (n=106) found low serum albumin was associated with increased post-operative transfusion rate (P=0.021) and reduced OS (HR =0.48; P=0.023). In summary, few recent studies have investigated the impact of low pre-operative serum albumin on PD outcomes but it would appear this is associated with worse short- and long-term outcomes.

CAR

CAR has been used as a marker for chronic inflammation and nutritional status. Few recent studies have investigated the impact of pre-operative CAR on PD outcomes. van Wijk *et al.* (99) (n=163, HR =1.745; P=0.004) and Haruki *et al.* (100) (n=113, P=0.049), found that, independent of staging, high CAR was a risk factor for reduced OS. No recent studies have investigated the impact of pre-operative CAR on peri-operative outcomes.

NLR

High pre-operative NLR is associated with poor prognosis in cancer patients across a wide spectrum of diagnoses, stages of disease, and courses of treatment (101). Although this is well described, the mechanisms behind this are poorly understood. Following a recent MA, Mowbray *et al.* (102) (8 studies, n=1,519) found high pre-operative NLR was associated with reduced OS (HR =1.77; P<0.001). The authors concluded that further studies are required to obtain a cut-off value which can be used for prognostic purposes (102). Sun *et al.* (103) (n=358) found OS was lower in patients with NLR >3.32 (HR =1.6; P=0.013).

Concerning peri-operative outcomes, Arikan *et al.* (104) (n=123) demonstrated that high pre-operative NLR was associated with increased overall morbidity following PD (41.9% *vs.* 14.8%, P=0.032). NLR had a high specificity but low sensitivity for predicting POPF (104). Other authors have also found this (105). In addition, Ida *et al.* (106) (n=208) found high NLR was associated with increased overall morbidity (OR =1.13; P=0.03) which contributed towards increased length of stay in those who experienced a complication (19 *vs.* 33 days, P=0.005). Huang *et al.* (107) (n=223) also concluded that patients who experienced complications were more likely to have a NLR ≥3.78 (3.38 *vs.* 2.24, P=0.006). Shen *et al.* (108) (n=835) found that NLR was significantly higher in those who experienced major morbidity (3.75 *vs.* 2.98, P<0.001). In summary, high NLR appears to increase peri-operative morbidity and reduce OS but a clinically significant threshold is yet to be defined.

Discussion

This review was carried out to consolidate the recent literature on pre-selected pre-operative factors and their impact on PD outcomes. *Table 1* summaries the impact of each variable on selected outcomes. An appreciation for the modifiable factors discussed may allow for patient optimisation prior to surgery. For example, a pre-operative review of all patients with diabetes or COPD by a specialist nurse, or the use of CPET to plan for peri-operative care, may result in reductions to morbidity rates. This, in turn, may increase the likelihood of patients starting and/or completing adjuvant chemotherapy. Routine assessment

Table 1 Selected pre-operative factors and their impact on selected PD outcomes

Pre-operative factor	Risk of POPF	Risk of SSI	Risk of DGE	Intra-operative blood loss	Length of stay	Peri-operative morbidity	Peri-operative mortality	Disease-free survival	OS
Demographic factors									
Advanced age (various thresholds)						↑	↑		
Male gender		↑		↑					
Pre-existing comorbidities									
Cardiac						↑	↑		
Respiratory						↑	↑		
DM									
Nutritional status									
BMI ≤18.5 kg/m^2					↑	↑	↑		
BMI ≥25 kg/m^2	↑	↑	↑			↑			
BMI ≥30 kg/m^2		↑		↑	↑	↑			
BMI ≥40 kg/m^2							↑		
Sarcopenia	↑	↑	↑			↑			↓
Myosteatosis									↓
Pre-operative imaging									
Heterogeneous tumour on CT								↓	
Hypoattenuating tumour on CT								↓	
Low enhancement change on dynamic contrast-enhanced CT								↓	↓
Rim-enhancement on MRI								↓	↓
Max. standardised uptake value >3.5 on PET-CT								↓	↓
Metabolic tumour volume >3 cm^3 on PET-CT								↓	↓
Total lesion glycolysis >10 g on PET-CT								↓	↓
Pre-operative therapies									
Biliary stenting	↑	↑	↑			↑			
NAT	↓		↑		↓	↓			↑
Pre-operative blood tests									
Bilirubin <7 mg/dL									↑
Bilirubin >20 mg/dL							↑		
Raised CRP (various thresholds)									↓
Albumin <35 g/L				↑		↑		↓	↓
Raised CAR (various thresholds)	↑					↑		↓	↓
Raised NLR (various thresholds)	↑				↑	↑			↓

Increased or decreased risk/survival compared to patients without the factor. References can be found within the article text. PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula; SSI, surgical site infection; DGE, delayed gastric emptying; OS, overall survival; DM, diabetes mellitus; BMI, body mass index; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; NAT, neoadjuvant therapy; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio; NLR, neutrophil/lymphocyte ratio.

of pre-operative CT imaging for sarcopenia and/or myosteatosis could prompt early dietetic input to reduce the pre-operative catabolic state, which may reduce the risk of anastomotic failure. To our knowledge, no prior studies have investigated the impact of treating myosteatosis on PD outcomes. We argue a study is required where patients with myosteatosis are randomised to either a specialised diet and exercise programme or standard care prior to surgery to investigate the impact on morbidity.

An appreciation for the non-modifiable factors discussed will assist the assessment of potential surgical candidates, allow clinicians to consider the appropriateness of PD, and result in more informed risk stratification and discussions with patients regarding risk and benefit. The influence of many of these factors on outcomes are limited to single-centre retrospective analyses and may not account for all confounding variables. The factors discussed were selected as they are currently being investigated by the RAW study. This is an international, multi-centre, retrospective analysis, which aims to investigate the impact of the variables discussed on patterns of recurrence and surgical outcomes following PD (NCT04596865). Results are expected in 2022.

This review has not aimed to answer a specific research question. Rather, it aims to provide the reader with a broad overview. Due to the number of topics covered, certain sections are very concise. Furthermore, we have chosen the variables which will be investigated by the RAW study and acknowledge that there are other important variables which affect PD outcomes e.g., smoking status. For simplicity, we have not included studies with less than 100 cases and limited our search to English language articles on the PubMed database. We acknowledge that out search methods will have been influenced by selection and publication bias and that there is a high degree of heterogeneity between the included studies which has not been formally addressed. Furthermore, sensitivity analysis, reporting bias and certainty assessments were not carried out. Meta-analysis has not been performed due to the large number of topics and studies.

Conclusions

Despite improvements to patient selection, surgical technique, and peri-operative care, PD continues to be associated with considerable morbidity. Even in the absence of surgical complications, few patients achieve long-term survival due to disease recurrence. A number of the variables discussed affect PD outcomes. Some of these may be used as prognostic indicators to assist patient selection, optimise patients pre-operatively and to guide risk/benefit discussions with potential surgical candidates. A robust study, which considers confounding variables, is required to further investigate these.

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