ROYAL AUSTRALASIAN
COLLEGE OF SURGEONS

Volume-outcome relationships

Pancreaticoduodenectomy

(Whipple Procedure)

Final report

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List of Terms

ACS NSQIP	American College of Surgeons National Surgical Quality Improvement Program
ANZHPBA	Australian and New Zealand Hepatic, Pancreatic and Biliary Association
ASA	American Society of Anesthesiologists
CD	Clavien-Dindo Classification System
CPG	Clinical practice guideline
CT	Computed tomography
DRG	Diagnosis-related group
ERAS	Enhanced recovery after surgery
HVH	High volume hospital
HVS	High volume surgeon
ICU	Intensive care unit
ISGPF	International Study Group of Pancreatic Fistula
ISGPS	International Study Group of Pancreatic Surgery
LOS	Length of stay
LPD	Laparoscopic pancreaticoduodenectomy
LVH	Low-volume hospital
LVS	Low-volume surgeon
MPL	Medibank Private Limited
MVS	Medium volume surgeons
OR	Odds ratio
OPD	Open pancreaticoduodenectomy
PICO	Population, intervention, comparator, outcome
PD	Pancreaticoduodenectomy
POD	Postoperative days in hospital
POPF	Postoperative pancreatic fistula
PPH	Post pancreatectomy haemorrhaging
RACS	Royal Australasian College of Surgeons
RR	Relative risk
TNM	Primary tumour, nodes, metastasis
VHVH	Very high-volume hospitals
VLVH	Very low-volume hospitals

Executive Summary

Background

Pancreaticoduodenectomy, commonly referred to as the Whipple procedure, is a complex surgical procedure used to treat peripapillary pancreatic tumours. Significant variation in clinical outcomes has been observed when Whipple procedures are performed in low- compared to high-volume centres.[1] Debate exists around whether volume thresholds should be used to qualify hospitals to perform complex operations like the Whipple procedure; however, the interaction between volume and outcomes is not well established. The objective of this review is to investigate and promote current best practice for the conduct of Whipple procedure, with a specific focus on the relationship between surgical volume and outcomes, by investigating the following research questions:

1. What surgical outcomes (i.e. hospital days, survival, or revision) could be used to appropriately represent the success or failure of the Whipple procedure?
2. How does the volume of Whipple procedures influence surgical outcome?
3. What initiatives have been successful in improving surgical outcomes – both internationally and in Australia?
4. What are the likely barriers to implementing a minimum volume framework in Australia and what mitigating factors should be considered?

Methods

This review was conducted using a combination of systematic methods (Research Questions 1 and 2) and rapid review methods (Research Questions 3 and 4), depending on the requirements of each question.[2,3] Peer-reviewed literature was identified through systematic and targeted searches of three biomedical databases (PubMed, Embase and the Cochrane Library) up to 14 September 2018. Studies were selected for inclusion based on pre-defined inclusion PICO (population, intervention, comparator and outcome) criteria by two independent reviewers. Meta-analysis was not appropriate due to the low level of evidence identified, and high degree of heterogeneity across study findings. Therefore, findings from the literature review have been narratively summarised and critically evaluated to identify key themes and commonalities.

Results and Conclusions

Key outcomes for Whipple procedure

Five broad categories of surgical outcomes were used to represent the success or failure of Whipple procedures in the evidence base: mortality, length of stay, complications, readmission/ reoperation and cost. There were substantial variations in terms of how these outcomes were defined and measured, especially around mortality and complications. These variations resulted in significant heterogeneity in the evidence base, making it difficult to compare one study to another.

Volume-outcome relationship for Whipple procedure

A total of 42 retrospective registry database review studies were identified that investigated the volume-outcome relationship for the Whipple procedure. Hospital and surgeon procedure volumes were inconsistently defined. Common thresholds to qualify a hospital as high-volume ranged from 20 to 40 cases per year (ranged from 5 to 200), whereas low-volume hospitals performed less than 10 procedures per year (ranged from 1 to 90). The discrepancy in the definition volume thresholds made it difficult to combine and compare results from different studies.

Mortality was reported in 33 studies, of which 23 found a statistically positive correlation between high procedure volume at hospitals and low mortality. When comparing the highest and lowest volume hospitals, the in-hospital mortality reduction can be as large as 6-fold. However, most of the studies did not adjust for potential confounding factors such as patient demographics, co-morbidities and hospital-related factors. Also, the high-volume benefits seemed to dissipate when the time horizon of mortality observation extended from in-hospital death to long-term survival. Surgeon volume had a similar impact on mortality as hospital volume, but a smaller number of studies focused on this association.

Length of stay was shortened when there was an increase in hospital or surgeon volume, as reported by 27 studies. When the number of days was counted between high- and low-volume hospitals, it appeared that high-volume centres could reduce hospital stay by up to three days. However, due to several issues around inconsistent length of stay definitions and potential confounding effects, these findings are subject to inconsistency and the between-study comparison may not be meaningful.

Reoperation and readmission outcomes were explored by 13 studies. Although some studies found an association between higher procedure volumes and lower rates of reoperation and readmission, these outcomes were affected by confounding effects and inconsistent definitions being used.

Although most of the included studies seemed to support a statistically significant association between high procedure volume (for both hospitals and surgeons) and better surgical outcomes for the Whipple procedure, substantial inconsistencies in outcome measures and significant methodological issues were also identified. A few of the most well-performed studies reported that, with appropriate adjustment for potential confounding effects, better surgical outcomes were driven by factors other than volume. Therefore, the causal relationship between high procedure volume and superior surgical outcome is uncertain for the Whipple procedure.

Initiatives for improving surgical outcomes

Most initiatives to improve the outcomes of Whipple procedures were related to common features of high-volume hospitals. It was also pointed out by several studies that those features were not exclusive to high-volume hospitals, and they could be replicated in low-volume settings to achieve good surgical outcomes. Those initiatives include:

- Providing evidence-based, personalised surgical care according to patients' risk profile, and to allow high risk patients to receive surgical care in hospitals with a higher level of staffing and equipment;

- Continuing to provide surgical training and skill exchanges for surgeons, to allow optimisation of technical skills and care protocols under different settings;
- Standardising postoperative care and promoting enhanced recovery after surgery to improve peri- and postoperative care to prevent severe complications and death;
- Supporting root-cause identification for mortality and resolving potentially life-threatening complications at an early stage;
- Promoting evidence-based hospital performance benchmarking instead of utilising hospital volumes as the sole indicators for hospital performance assessment;
- Establishing partnerships between high- and low-volume hospitals to foster a stronger health network and cater to patients with different needs.

Barriers to implementing minimum volume threshold in Australia

The main barriers towards implementing a minimum volume threshold included concerns regarding the use of volume as a sole indicator of hospital quality, the loss of access to services associated with Whipple procedures in rural areas, increased high-volume hospital burden, disruption of the market, and burden on patients (particularly rural) due to travel requirements. In contrast, considerations around a minimum volume threshold may be facilitated by a number of levers such as greater access to resources, ease of implementing guidelines and standardised procedures, improvements in surgical training, patient education and cost savings.

Conclusions

Overall, the evidence base has demonstrated a statistically significant association between high procedure volumes and better clinical outcomes for Whipple procedures. However, the included studies exhibited substantial heterogeneity and significant methodological flaws. These limitations prevent the establishment of a meaningful hospital or surgeon volume threshold for Whipple procedures within the Australian context. Non-volume initiatives could also improve surgical outcomes, in both high- and low-volume settings. It may not be sufficient to utilise procedure volumes as the sole indicator for patient outcomes of Whipple procedures. With adequate support from hospital staffing and facilities, successful Whipple procedures can be achievable regardless of the volume; whether this is economically feasible in Australia is subject to further investigation. As a result of this review a number of key recommendations to optimise the outcomes of Whipple procedures were developed, which incorporate patient, surgeon, hospital and governance perspectives.

Background

The Royal Australasian College of Surgeons (RACS) and Medibank Private Ltd (MPL) recently produced several reports into surgical variation for high-volume procedures.[4] These initial reports examined variation within MPL's administrative data-set. Notably, the report on General Surgery highlighted the impact of surgeon volume on variation, with low-volume surgeons having greater variation in outcomes compared to surgeons with a high caseload.[5] As part of the ongoing review of surgical variation, the next targeted area of inquiry with potential areas for system improvement is low-volume, high-risk procedures.

Pancreaticoduodenectomy, commonly referred to as the Whipple procedure, is a complex surgical procedure used to treat uncommon peripapillary pancreatic tumours.[6] Whipple procedures carry a mortality risk ranging between 2% and 16%, with variation noted both internationally,[1] as well as within States in Australia.[1,7] As suggested in a Queensland Health report, the need for Whipple procedures is likely to increase, with the primary driver being the increased proportion of the population being aged over 65 years;[1] a trend that has been observed throughout Australia.[8]

The relationship between procedure volume and patient outcomes for Whipple procedures is the subject to ongoing debate. In 2017, MPL funded 411 procedures under the H01 "Pancreas, Liver and Shunt Procedures" diagnosis-related group (DRG), which includes Whipple procedures, with the annual hospital volume ranging from 1 to 42 separations (personal communication Dr D. Rankin, April 2018). The Queensland Health report investigated the impact of hospital volume and found that those performing less than three procedures per year have a significantly higher level of variation in clinical outcomes. For Western Australia, the Health Department has mandated that all pancreatic surgeries be performed at one of two metropolitan cancer centres to ensure both the surgical team and setting has sufficient volume;[8,9] however, such centralisation may create a barrier to treatment for those living in non-metropolitan areas.

Based on the prior experience of RACS Research and Evaluation in reviewing the impact of surgeon/hospital volumes across a number of surgeries, including the Whipple procedure,[10-15] RACS and MPL propose that the 'rapid review' method will provide a rigorous and cost-effective approach to the investigation of surgical/hospital volume on the clinical variation associated with the Whipple procedure.

Research questions

1. What surgical outcomes (i.e. hospital days, survival, or revision) could be used to appropriately represent the success or failure of Whipple procedure?
2. How does the volume of Whipple procedures influence its surgical outcome?
3. What initiatives have been successful in improving surgical outcomes – both internationally and in Australia?
4. What are the likely barriers to implementing a minimum volume framework in Australia and what mitigating factors should be considered?

Methods

This review was conducted using a combination of rapid and systematic literature review methods. Research Questions 1 and 2, regarding the impact of procedure volumes and its associated factors on surgical outcomes of the Whipple procedure, was evaluated using a comprehensive systematic review method. The rapid review method, which is an adaptation of a comprehensive systematic literature review technique, was used to address Research Questions 3 and 4. The rapid review format allows the timely identification of the best quality evidence at the highest level to answer the research questions but may not include the entirety of the available evidence on the topic.[2,3]

Literature search strategy

Peer-reviewed literature

Peer-reviewed literature was identified through a combination of systematic and targeted searches of three biomedical databases (PubMed, Embase and the Cochrane Library) up 14 September 2018. The systematic literature search was used to identify most of the evidence included in this review (see Appendix 1 for full details of the search strategy); however, the systematic search strategy was primarily designed to identify the available evidence for Research Questions 1 and 2. To ensure the evidence identified for the remaining research questions was comprehensive, targeted keyword searches of PubMed were conducted to identify additional literature that may have been missed by the primary literature search. The search results were exported into reference management software for study selection (EndNote X7).

Clinical practice guideline and grey literature searches

Separate searches were conducted to identify clinical practice guidelines (CPGs) and other literature resources (governmental publications and other non-peer reviewed literature) not indexed in the biomedical databases. These resources were primarily sought to supplement the peer-reviewed evidence supporting Research Questions 3 and 4. The CPGs and grey literature were sought from a range of grey literature databases, listed in Appendix 1. An article was deemed to be a CPG if it met pre-specified criteria adapted from Graham et al.[16] CPGs published after 2013 were reviewed, since CPGs are considered out of date five years after publication.[17,18] Identified CPGs were shortlisted by one researcher based on their publication date and relevance to the research questions.

Study selection

The inclusion criteria for this review were based on the relevance of the study population, intervention, comparator, outcomes (PICO) and design to the proposed research questions.[19] Studies were selected by two authors independently (MV and NM) using the pre-defined inclusion criteria, with disagreements settled via consensus. The results of the study selection process are presented in Appendix 2. All published comparative studies were included for Research Questions 1 and 2. Published literature for Research Questions 3 and 4 was also identified and prioritised for inclusion. Priority was given to higher level evidence (systematic reviews, and randomised controlled trials where available). The inclusion criteria for published literature are

summarised in Table 1. For CPGs, priority for inclusion was given to CPGs from Australia and New Zealand. Studies that were excluded at full-text review are listed in Appendix 5.

Table 1 Inclusion and exclusion criteria

PICO element	Inclusion/exclusion criteria
Population	Patients who underwent Whipple procedures for any indications, but excluding emergency procedures
Intervention	Whipple procedures performed under a high-volume setting
Comparators	Whipple procedures performed under a low-volume setting
Outcomes	Any patient related outcomes†

Note: † = all outcomes are reviewed, and the most relevant outcome(s) are determined by Research Question 1.

Data extraction

Data extraction was conducted by one of two authors (MV/JHJ) and checked for accuracy by other authors (NM/AS), using a standardised extraction template. Data were extracted for study characteristics, procedure-related factors (including procedure volumes), and all patient-relevant outcomes.

Data analysis and synthesis

Based on the project scoping and the research protocol, quantitative synthesis of the data (meta-analyses) was not proposed due to the level of the evidence base being relatively low (level III studies). For this topic, it is very unlikely to design and conduct a randomised controlled trial to compare high and low procedure volumes on surgical outcomes. This means most of the included studies are likely to be observational studies, which potentially suffer from a higher risk of bias and confounding effects. Therefore, findings from the literature review are narratively summarised and critically evaluated to identify key themes and commonalities. Quantitative results were extracted, summarised and plotted to visualise the effect sizes across the included studies.

Review Working Group

In conducting this review, the Surgical Director of RACS Research and Evaluation provided clinical input to guide research staff. In addition, RACS Fellows and representatives from MPL participated as members of a Review Working Group (Appendix 4). This group provided guidance and feedback on the scope of the project and the report.

Results

Research Question 1

What surgical outcomes (i.e. hospital days, survival, or revision) could be used to appropriately represent the success or failure of Whipple procedures?

Evidence highlights

- The association between volume and mortality for Whipple procedures was the primary focus of the evidence base (n=42 studies). All studies except one[20] investigated mortality outcomes in some form, including short-term (in-hospital, n=26), medium-term (30-, 60-, 90-day, n=17) and long-term patient survival (n=4). Some studies investigated more than one mortality outcome (n=6).
- Over half of the studies (62.5%) focusing on mortality outcomes did not investigate potential confounding factors (no confounding adjustment) or did not present sufficient information of which factors and how those factors could impact on the mortality outcomes.

Summary of clinical outcomes reported in the literature

Forty-two studies were identified that investigated the outcomes of Whipple procedures. Five broad categories of surgical outcomes were used to represent the success or failure of this procedure in the evidence base: mortality, length of stay, complications, readmission and reoperation. There were substantial variations in terms of how these outcomes were defined and measured, especially around mortality and complications. These variations resulted in significant heterogeneity in the evidence base, making it difficult to compare one study to another. Therefore, quantitative synthesis of the data via meta-analysis was not performed in this review. Some key issues around these outcomes are discussed in detail below.

Table 2 Summary of issues with the clinical outcomes reported in the included studies

Outcomes in the included studies	Inconsistencies in how outcomes were measured	Issues in analytical methodologies	Potential impact
Mortality	• Three mortality outcomes explored: i. in-hospital ii. medium term (30-, 60- and 90-day) iii. long-term survival (up to 5 years) • Definitions of different mortality outcomes were not explicitly reported in most studies. • Information regarding causes and time of death was lost due to the simplifying the mortality outcome to a dichotomised variable (alive or dead) .	• Potential confounding adjustments were considered by less than half of the included studies. • Factor adjustments were subject to substantial variations regarding quantity and methods. • A range of statistical models with different complexities were used for different aspects of the data. Some models were oversimplified prone to significant limitations due to potential confounding effects.	• All studies were subject to some level of risk of bias due to potential confounding from external factors not measured/adjusted. • Between study comparisons were difficult due to variations in outcome and analytical methodologies; • Meta-analysis was not feasible due to the substantial risk of bias and heterogeneity.

Outcomes in the included studies	Inconsistencies in how outcomes were measured	Issues in analytical methodologies	Potential impact
Length of stay (LOS)	•A large proportion of the included studies did not specify how LOS was measured. •When the LOS definition was reported, a variety of LOS was measured, which included TAD, POD IHD etc.	•LOS days were analysed differently: some studies treated as a continuous variable whereas some other studies dichotomised LOS days into groups and treated as a categorical variable. •Most of the studies did not adjust for confounding factors.	• Substantial inconsistencies were expected for this outcome due to methodological issues. • Between study comparisons were difficult due to variations in outcome and analytical methodologies. • Meta-analysis was not feasible due to the substantial risk of bias and heterogeneity.
Complications	• A variety of different graded complication scores were reported. • Specific complications were also considered but with different definitions and clinical context. • There has been changes and standardisation processes in how complications were defined (e.g. the clinical relevancy of fistula)	• Complications were only considered by a small number of studies. • Complications were both considered as an outcome and as factors in predicting mortality. • Confounding adjustments in complications were very poor.	• All issues identified from the previous outcomes apply to complications as well. • When complications were considered as a predictor of mortality, it masked the impact of volume variables.
Reoperation and readmission	• The timeframe of reoperation and readmission were inconsistent. • Definitions of readmission and reoperation were not provided in most of the studies. The reason for readmission might be different across different studies.	• Potential confounding adjustment was not common conducted when investigating reoperations. • Only one study did not adjust for confounding factors when the readmission outcome was investigated.	• All issues identified from the previous outcomes apply to complications as well.

Abbreviations: **IHD** = in-hospital days, **LOS** = length of stay, **POD** = postoperative days, **TAD** = total admission days.

Mortality outcomes

Due to the challenging and complex nature of the surgery, Whipple procedures are associated with a high risk of mortality. When studying the volume-outcome associations, mortality was one of the most investigated outcomes in the evidence base. Except for one study by Shi et al.,[20] the remaining 41 studies included patient death as their outcome. Overall there were five different mortality outcomes reported in the evidence base which can be grouped into three categories.

Short-term: In-hospital mortality

The most widely reported mortality outcome was in-hospital mortality, also referred to as inpatient mortality by some studies.[21-25] Although the explicit definition of in-hospital mortality was not given in most of the studies, it was generally perceived as patients' death during the hospital stay, prior to discharge. This outcome was investigated in 25 primary studies as a dichotomised outcome (i.e. patients are either dead or alive). This dichotomisation removes the information of length of postoperative hospital stay so that the in-hospital

mortality may be captured under different time windows. In routine practice, postoperative recovery of the Whipple procedure take place in general ward for seven to nine days before discharge.[26,27] Where an intensive care unit (ICU) admission is required for any reason, patients may need to spend one or more days under intensive care.[28,29] Therefore, this is the period where in-hospital mortality may occur, and this observation period is relatively short (less than 14 days).[22] However, in some cases a prolonged length of stay may occur which could also be associated with a high chance of in-hospital death due to major complications. This is sometimes referred as failure-to-rescue. This is a compound clinical endpoint which was explored in several the included studies.[30-32] This outcome will be discussed separately. In most of the studies (n = 18 out of 25), the patients' average length of stay was also investigated.

Medium-term: 30-day, 60-day and 90-day mortality

Seventeen studies investigated longer-period mortality outcomes. A total of ten studies investigated 30-day mortality,[33-42] two studies investigated 60-day mortality,[43,44] and eight studies investigated 90-day mortality.[30,32,39-41,45-47] Three studies investigated multiple time points.[39-41] The definition of medium-term mortality was scarcely provided. When provided, these three mortality outcomes were defined as death from any cause postoperatively at 30, 60 and 90 days. It appeared that medium-term mortality outcomes are investigated mostly by studies published from 2010 and later (14 out of 17). One article argued that with the improvement of patient care, short-term mortality has been greatly reduced, hence long-term mortality outcomes may be more appropriate to reflect the quality of surgery.[32]

Long-term: Patient survival

Four studies[29,32,41,48] investigated the survival of patients after the Whipple procedure. The survival outcome is a time-to-event outcome, which incorporates both the occurrence of death (the "event") and the "time" elapsed before patients' death occurred. Therefore, the survival from Whipple surgery describes the "hazard" of postoperative death from any cause at any given time. Two of the studies investigated relatively short-term survival: Gooiker and colleagues[41] investigated one- and two-year survival, whereas Birkmeyer and colleagues[48] observed three-year survival after the Whipple procedure. The study by Schell et al.[29] and van der Geest et al.[32] investigated longer patient survival after receiving the Whipple procedure, up to five and eight years respectively. Although long-term survival is an important outcome for patients, the success of Whipple procedures might not be the only factor attributable to the survival of patients in the long term. As most recipients of the Whipple procedure are cancer patients, the survival outcome is a better outcome to describe the success of overall cancer management. Also, survival analysis data are complex and could be greatly influenced by patient loss-of-follow-up (censoring). Therefore, the survival outcome was not chosen by most of the included studies.

Analytical methodologies for mortality outcomes

Although there are several distinct mortality outcomes explored in the evidence base, they can be categorised into two broad groups: 1) dichotomised outcomes which include in-hospital, 30-day, 60-day and 90-day mortality, and 2) survival outcome where death occurrence and time-to-death are both considered. Typically, different mortality rates were compared across hospitals or surgeons using different volume tiers as the main

predictor. For the outcome, odd ratios (ORs) or relative risks (RRs) were produced as the comparative result. With or without considering any potential confounding factors, logistic regression models are used to control other predictors such as age, gender, co-morbidities and others. When confounding factors were ***not*** considered, naïve statistical tests (primarily the Chi^2 test) were used to investigate the associations between procedure volumes (as categorical variables) and mortality. For survival outcomes, hazard ratios (HRs) were produced as the outcome of the survival analyses. Confounders were incorporated into the model using the Cox-proportional hazard model whereas the naïve Kaplan-Meyer method was also used when confounding was not considered, resembling the simple statistical tests in binary mortality outcomes. It is important to recognise that all studies included in this review were non-randomised, non-controlled observational studies. Therefore, the result of the analysis was susceptible to potential bias due to confounding effects, especially when non-volume factors were not controlled. As seen in many of the included studies, an inclusion or an exclusion of certain factors may greatly influence the overall findings of the study.

Evidence profiles and bias assessment of mortality outcomes

Fourteen studies did not adjust for any potential confounders for mortality outcomes: ten studies investigated in-hospital mortality without involving any other factors other than procedure volumes,[21,26-28,47,49-53] three were on 30-day mortality,[33,35-37] and two on 90-day mortality[46,47] with one by Hyder and colleagues (2013) also on in-hospital death. One survival analysis by Schell and colleagues did not adjust for confounders but some data rearrangement was performed to overcome the issue.[29] Fourteen studies incorporated some level of adjustment in the analyses but the effect sizes of the adjusted factors were not reported in the publication. Seven studies investigated in-hospital mortality,[22,24,48,53-56] four investigated 30-day mortality,[34,38-40] while two also included 90-day mortality as their outcomes.[39,40] Only one study by Kennedy et al.[44] reported 60-day mortality. In total, there were 25 studies (out of 40 included studies, 62.5%) that did not adjust for confounding factors or provide sufficient information regarding the outcome of the confounding adjustment for mortality outcomes.

The remaining 14 included studies had variable levels of adjustment incorporated into their analyses. The detailed impact of cofactors on mortality will be discussed together with volume in the next section, to answer Research Question 2. Overall, in-hospital mortality was addressed by nine studies.[25,31,42,57-62] All except one[42] reported that older age contributed significantly to higher mortality. Gender was not a factor in most of the studies except two,[31,58] which reported that male patients were associated with higher in-hospital mortality. The presence of comorbidities (by Charlson comorbidity index, American Society of Anesthesiologists (ASA) score or specific conditions) was found to increase in-hospital mortality in four studies.[25,57-59] Some other factors such as cancer types, teaching hospitals and surgical techniques were found to have a statistically significant impact on in-hospital mortality; however, they were only identified in individual studies. For longer mortality including 30-, 60- and 90-day as well as survival outcome, similar findings were also observed. Older age was significantly associated with higher mortality by day 90 and up to two years.[30,32,41] Worse ASA status and more advanced pancreatic cancer status (TNM stages) was associated with higher 60-day mortality and worse long-term survival.[32,43]

Length of stay (LOS)

Outcome definition variations

Twenty-six studies investigated the impact of procedure volume on hospital LOS. However, there was substantial variation in how hospital LOS is defined. Where the definition was provided, postoperative days in hospital (POD) was the most widely utilised LOS definition (n = 12).[21,26-29,34,35,44,49,50,58,63] Three studies also compared ICU days against different volume settings.[28,29,55] Lidsky and colleagues described the LOS as "surgical in-patient days".[40] The other two studies defined LOS as "total length of admission to the hospital",[47,59] and Hyder and colleagues further elaborated the definition as the length of index admission (i.e. excluding re-admission). Issues concerning total hospital days over postoperative days were primarily regarding the inclusion of preoperative stays. When the LOS differences between different volume settings or other confounding factors were small, the extra preoperative days may lead to different interpretations.

Ten studies did not provide any definition of LOS,[20,22,33,42,51-54,56,62]. For these studies the most significant issue that could potentially prevent inter-study comparisons is around how readmission is recorded and distinguished in the analysis. Since most of the studies conducted a retrospective review of clinical registries or databases, how the indexed admission and readmission were coded could significantly impact on the data; however, this aspect was clear in most of the studies. Where the indexed hospitalisation and readmission days were combined as total hospital days, total hospitalisation days may be inflated if readmission occurred. Therefore, the interpretation of the study outcomes could be different to those only including indexed or postoperative LOS.

Another variation in this outcome is how length of stay was processed as the outcome. In most of the included studies LOS was counted by the number (i.e. a continuous variable). Therefore, results of these studies are presented by an increased or a decreased number of hospital days. In two studies, however, LOS days were dichotomised into either above or below 14 days where spending over 14 days in hospital were considered as prolonged LOS.[22,53] Another study by Kagedan et al. categorised LOS into percentiles and the prolonged LOS was defined as postoperative hospital days longer than the 75th percentile of the studied patient population.[30] Therefore the results of these three studies are in form of odds ratios, hence not comparable to the remainder of the other studies.

Confounding adjustment

This outcome was not as well-adjusted as mortality. Only 13 studies were adjusted for confounding and four of them presented with numeric results of the adjustments.[20,30,53,59] Across the four studies, older age was consistently associated with a longer LOS. The presence of comorbidity was also associated with a longer LOS in three studies.[20,30,59] Only Shi and colleagues found that being female was associated with a shorter LOS.[20] Schneider and colleagues also identified that teaching hospital, health insurance status and race were also associated with prolonged length of stay over 14 days.[53]

Complications

Postoperative complications was the other commonly investigated outcome in the evidence base. It was primarily described by two streams: 1) overall complication severity using Clavien-Dindo (CD) grades and classifications, and 2) the occurrence of specific complications such as fistula development, bile leak or haemorrhage.

Overall postoperative complication severity

The overall severity of postoperative complications was described using the CD Classification System. The system graded the severity of complications into five categories, where for Grade III and IV two sub-categories were also available to further characterise complications requiring different levels of intervention. A complication graded III and higher was considered a major complication where pharmacological interventions could no longer resolve the event; hence, surgical or image-guided intervention is warranted. Six studies adopted the CD Classification System to categorise complications into either major or minor using Grade III and above as the threshold.[26,31,34,43,44,46] In addition, the study by Stella et al.[26] also investigated the effect of different volume on grade changes.

A slight variation in Grade threshold was also observed in one study. Instead of using Grade III like others, Addeo and colleagues[43] defined major complications as being Grade IIIb and higher (inclusive), where the sub-scale "b" indicated that the intervention must be under general anaesthesia. This is a more restrictive definition which could mean more severe complications than the general Grade III cut-off. An older study by Nordback et al.[62] did not use the CD Classification to define complication severity. Instead, postoperative recovery was dichotomised into either uncomplicated recovery or having complications where explicit definitions on these outcomes were not provided.

None of the studies above provided sufficient information regarding how confounding factors were adjusted. Further, complications as an earlier and more direct outcome of Whipple procedures were also considered as a factor contributing to mortality. The simultaneous consideration of major complication and patient death was defined as "failure-to-rescue". This is discussed later in this section as a separate outcome measure.

Specific complications *(including fistula, delayed gastric emptying and haemorrhage)*

Fistula development delayed gastric emptying and postoperative haemorrhage are all debilitating complications for Whipple surgery. In particular, pancreatic fistula (POPF) is regarded as the major complication and is related to elevated postoperative mortality for Whipple procedures.[43] These complications were included as specific outcomes and investigated by a number of studies in the evidence base. It is worthwhile to note that these outcomes have been studied only in the past 10 years even though the evidence base spans over 25 years. This might be related to an international standardisation process for how these outcomes are defined. In 2005, the International Study Group of Pancreatic Fistula (ISGPF) unified the definition of POPF[64] which was also validated[65] and updated[66] in recent years. Similar standardisation processes were also observed for delayed gastric emptying (DGE) and post-pancreatectomy haemorrhaging (PPH) through the International Study Group of Pancreatic Surgery (ISGPS).[67] Therefore, more reliable comparisons can subsequently be made for these complications between institutions and studies.

Postoperative pancreatic fistula

This outcome was identified and investigated by ten studies. Except two where explicit definitions of fistula was not provided,[29,54] the other eight studies all used the ISPGS definition of fistula.[21,26,31,34,35,43,46,53] Postoperative pancreatic fistula, based on the ISGPF definition in 2005, was defined as "an abnormal communication between pancreatic ductal epithelium and another epithelia surface containing pancreas-derived enzyme-rich fluid". Further, three discrete grades (A, B and C) were used to characterise the POPF severity, with grade A being considered less clinically relevant.[66] Despite this standard definition, a recent ISGPF publication acknowledged potential issues and confusions of the 2005 definition, hence updated the POPF to be more specific and restrictive.[66] When reporting POPF rate, it has not been clear whether the POPF was only the clinically relevant ones (Grade B and C) or inclusive of all grades. Studies which utilised the all-inclusive definition of POPF would report rates twice as high as those only on Grade B and C.[66] For clarity, recent studies started to report clinical-relevant POPF (CR-POPF) as a distinct outcome. The CR-POPF was acknowledged and reported specifically by van Rijssen et al.[31] and Addeo et al.,[43]; both studies focused heavily on postoperative complications and fistula incidence in particular. Moreover, none of these studies appropriately adjusted for confounding factors in their analysis of POPF. Therefore, the comparability of outcomes across these studies may be severely limited.

Other specific complications

As described earlier, DGE and PPH were also investigated among the included studies, and these two outcomes also experienced a standardisation process similar to POPF. Among the studies on DGE (n = 7) and PPH (n = 4), four of them utilised the standardised ISGPF DGE and PPH definitions[31,34,46,68] three did not provide any information regarding how DGE is defined, and one did not define PPH.[29] None of the studies adjusted for confounding factors during the analysis.

Other than DGE and PPH which have standardised definitions, four studies also investigated volume-effect on other outcomes such as surgical site infections[46,54,68] and bile leaks.[31,68] Since they were rarely considered and less severe compared to other outcomes discussed, these outcomes will not be considered as core outcomes for Research Question 2.

Readmission and reoperations

Readmission and reoperations were also investigated in the evidence base. Reoperations were investigated in seven studies[26,30,34,46,54,62,68] and readmissions were included by six studies as their outcome.[22,28,30,33,40,47] Among the seven studies investigating reoperation rates, four of them did not adjust for any confounding factors during the analyses[26,46,54,68] whereas it was not clear in one study.[62] For the readmission outcome, all (n = 5) except one included studies[33] did adjust for confounding factors, and one study investigated 90-day readmission[30] instead of the 30-day outcome.

Composite outcome: failure-to-rescue

While mortality was the primary clinical outcome in the included studies, different causes of patient death were not considered. As a result, these studies did not differentiate mortality due to Whipple procedures from

other causes (tumour progression, co-morbidity etc.). A number of severe complications previously mentioned could potentially be life-threatening, and these complications are related to the higher mortality for Whipple procedures. Therefore, it is important to recognise early signs of these severe complications.

Deaths due to severe complications are referred as “failure-to-rescue”. This is a composite clinical endpoint: a failure-to-rescue case is established only when postoperative death and a major complication occur at the same time, and the cause of death was driven by the surgical complication(s). The importance of this clinical outcome was highlighted in several studies, but only one study by van Rijssen and colleagues investigated this outcome.[31] In this study, failure-to-rescue was defined as postoperative in-hospital death due to major complications with a CD morbidity score greater or equal to three. This means that the mortality cases were not included when the death was not caused by major complications. Therefore, the finding of the study may not be comparable to those that measured all-cause mortality.

Several studies considered complications as predictive factors for mortality. When complications were incorporated into statistical models, most of the studies found failure-to-rescue to be the most significant cause of death. This also highlighted the fact that successful resolution of complications could lead to a substantial reduction in mortality. Therefore, the analysis of failure-to-rescue may be more relevant clinically in future investigations.

Research Question 2

How does the volume of Whipple procedures influence its surgical outcome?

Evidence highlights

- The evidence base is large, complex and was conducted over a long period of time.
- There were significant discrepancies in how high- and low-volume hospitals or surgeons were defined. When volume tiers (for hospital or surgeons) were defined, a statistically significant result was more likely to be found between the highest and the lowest tier. The bigger the difference in volume, the more consistent the findings were.
- The evidence base showed a clear association between higher hospital volume and lower mortality for the Whipple procedure. However, these positive findings were likely to be restricted to their own study context.
- Length of stay was shorter in high-volume hospitals than low-volume ones. Most of the studies did not adjust for any confounding factors when investigating this outcome.
- Confounding adjustments were poorly conducted in most of the studies. The association between procedure volume and patient outcomes was less apparent in studies that adjusted for confounding factors.

Summary of results

Procedure volumes of hospitals and surgeons were defined differently across the studies included in the evidence base. The volume cut-offs were dependent on the study context, meaning that a 'high-volume' hospital or surgeon in one study could be classified as 'low-volume' in another study. Therefore, it is difficult to compare the volume-outcome associations across different studies.

In-hospital mortality was the most widely investigated outcome in the evidence base. Other mortality outcomes including 30-day, 60-day and 90-day mortality were also investigated in some studies. Although proportionally more studies identified the association between higher volumes and lower mortality (of any type), the volume cut-offs used in the comparisons were different from one study to another. Also, the evidence base was potentially confounded due to the lack of covariate adjustment.

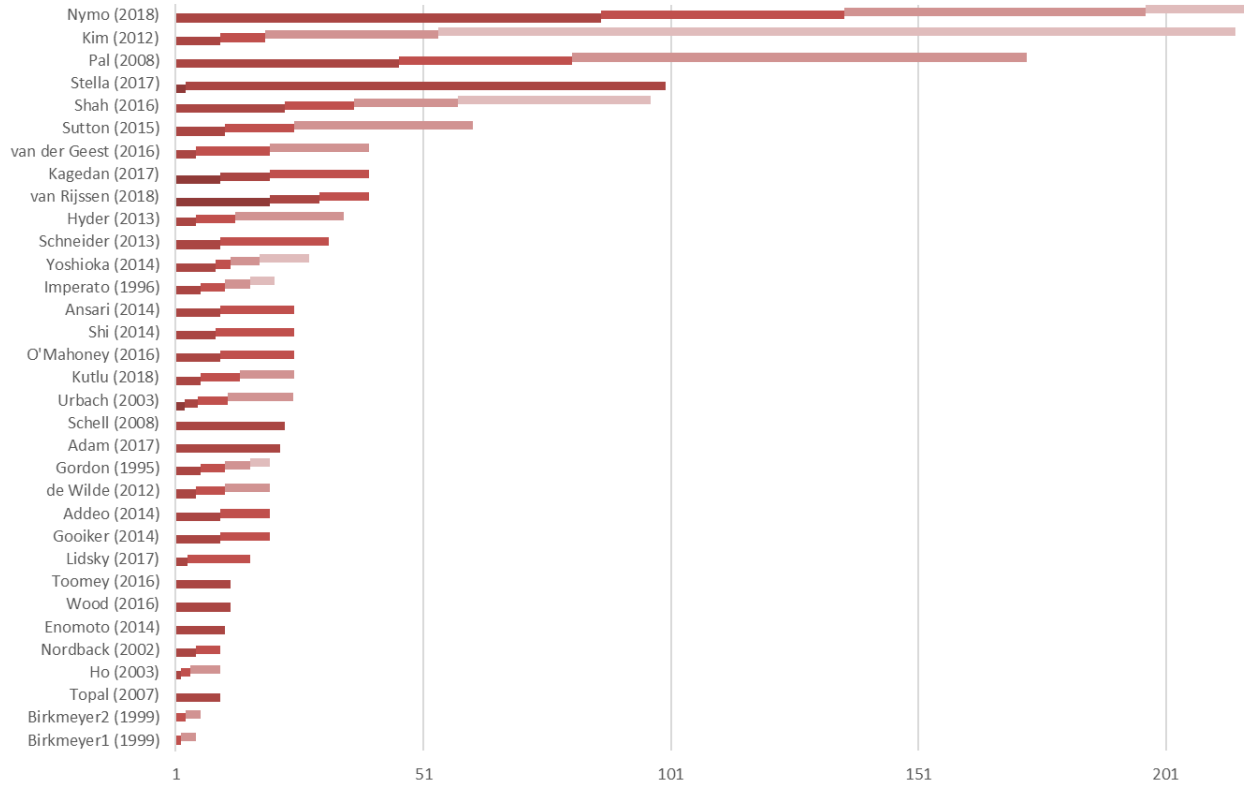
Other outcomes such as length of stay, readmission and reoperation rates were also explored in the evidence base. Similarly, there were more studies with the positive findings (statistically significant association between procedure volumes and outcomes) but the associations were based on heterogeneous volume cut-offs and diverse clinical background information.

Therefore, a clear volume-outcome relationship could not be established from the current evidence base. A minimum procedure volume threshold for better patient outcomes of either hospitals or surgeons could not be determined.

Hospital and surgeon volumes

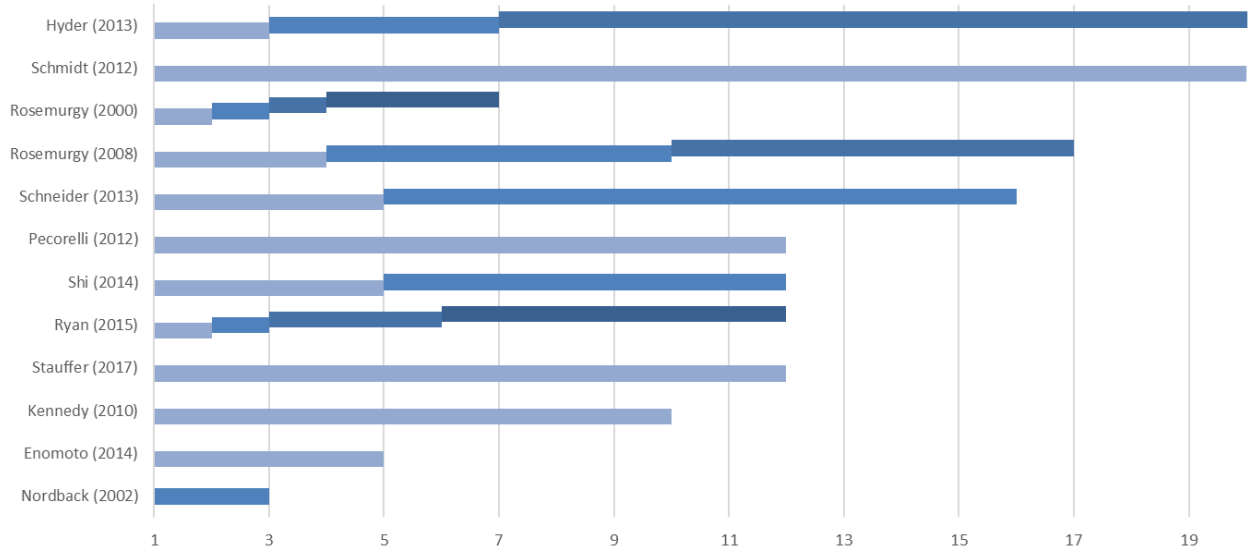
Based on the included studies, procedure volumes of different hospitals and surgeons were investigated against a variety of different clinical outcomes. In most of the studies, procedure volumes of hospitals and surgeons were categorised into different tiers based on the annual procedure caseload, and the studies nominated different tiers with group names such as “very high-volume hospitals (VHVH)” or “medium-volume surgeons (MVS)”. The categorisation of hospitals or surgeons were characterised by either *a priori* defined criteria, or the *post hoc* ranked percentiles (quartiles and quintiles). To better illustrate characteristics of hospital and surgeon volume cut-offs, two waterfall bar charts were produced to visualise variations of hospital and surgeon volume thresholds in Figure 1 and Figure 2. Both hospital and surgeon volume upper cut-offs were plotted in one graph, represented by coloured legends. Different colour gradients represented by staggered bars were used to demonstrate different volume tiers nominated by each study. Due to limitations of the plot, for studies where the last volume tiers were not bounded by a ceiling (e.g. hospital volume over 60 per year), those tiers were not visible from the chart. In other words, the end of each bar represented the upper thresholds of the volume tiers, not the actual last tier. Further, some studies treated volumes as continuous variable, or did not provide sufficient information on how volume tiers were produced. Those studies were not plotted and only described via context.

Figure 1 Procedure Volumes cut-offs by Hospitals



Example interpretation: The study by Kim and colleagues (2012), the second study from the top, has 5 volume categories (hence 4 step-ups): VLVH (<10/year, 1st step-up), LVH (10-18/year, 2nd step-up), MVH (19-35/year), HVH (54-111/year) and VHVH (>215/year, as the end of last bar). Colour gradients represent different cut-offs.

Figure 2 Procedure Volumes cut-offs by Surgeons



Example interpretation: The study by Ryan and colleagues (2015), the fifth study from the bottom, has 5 volume categories (hence 4 step-ups): VLVS (>1/year, 1st step-up), LVH (2-3/year, 2nd step-up), MVH (4-6/year), HVH (7-11/year) and VHVH (>12/year, as the end of last bar). Colour gradients represent different cut-offs.

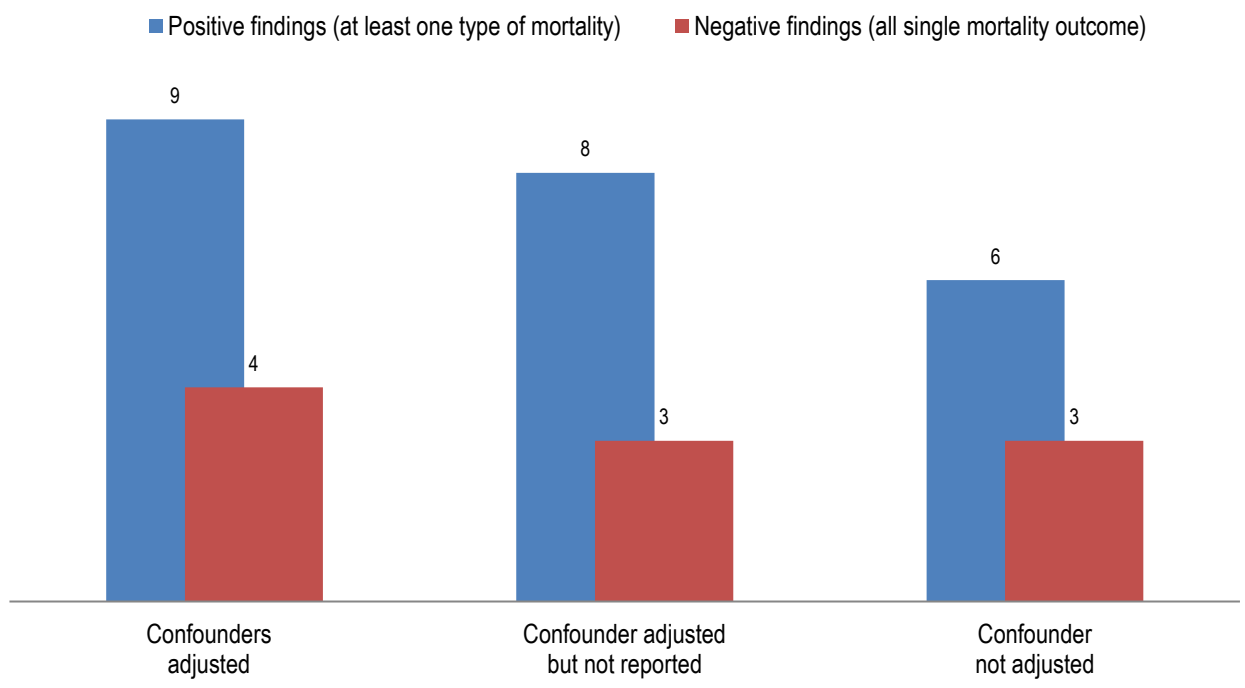
Across all the included studies, the definition of a high or low-volume for a hospital or a surgeon was diverse. For hospitals, it appeared that most of the studies characterised hospitals as high-volume tiers when annual volumes exceeded 20 to 40 cases. The threshold for low-volume hospital tiers was mostly smaller than 10 cases per year. Seven studies only dichotomised hospitals into either high or low so that only one volume cut-off was used.[26,27,29,33,50,54,59] Three studies defined a hospital with annual volume over 100 to be high-volume hospitals.[37,45,60] The study by Kim was a Korean study and hospital data was retrieved at a national level. The high case load for certain hospitals may be due to high population density. Nevertheless, there was only a single hospital defined as "very-high-volume" (caseload average = 215/year) and three "high-volume" hospitals (case load average between 54 and 111/year). Most of the hospitals were low (n = 20 cases) and very low (n = 92 cases). The study by Pal et al. was a UK study.[37] The study only reported limited detail regarding how hospital and surgeon caseloads were calculated. It was unclear whether the caseload was aggregated over years or averaged into annual figures. For four hospitals which were defined as the "largest" volume hospitals, the caseload range was between 173 and 317.

Surgeon volumes were reported with less variation. Among the 12 studies on surgeon volumes, the average upper threshold for high-volume surgeons was over 13 per year. Most of the studies defined a high-volume surgeon as performing at least 10 Whipple procedures per year. Only two studies required surgeons to perform over 20 Whipple procedures per year to be classified as high-volume surgeons.

Outcome: Hospital volumes and mortality

For mortality (including all types), which was the most investigated outcome by 33 studies, 23 of them showed an inverse relationship between hospital volume and mortality for the Whipple procedure. The other 10 studies found no associations. As analysed previously, most of the studies did not perform adequate confounding adjustment (n = 20). When the confounding factors were adjusted, more studies found an inverse relationship (17 out of 23, including 8 adjusted but effect size not reported). Patient mortality was analysed according to a range of different time windows. The study numbers were tabulated and presented in Figure 3 below. Among the included studies, 19 considered in-hospital mortality whereas 8, 1, and 7 studies analysed 30-, 60- and 90-day mortality respectively. Four articles investigated long-term survival using the time-to-event approach. Seven included more than one type of mortality outcomes their studies, and confounding adjustment was study-specific. Among the seven articles, two studies had no adjustment whatsoever,[29,47] and another three did not present effect sizes on any factors adjusted.[39,40,42] The study by Gooiker et al.[41] only adjusted the long-term survival but not the 30- and 90-day mortality. The study by van der Geest et al.[32] is the only one which presented the effect sizes for all predictors (including confounders) for both 90-day mortality and long-term survival analysis. Results of all the included studies were extracted to Table 10 (Appendix 3).

Figure 3 Hospital volumes and mortality outcomes by study numbers



Note: Positive finding = a positive relationship between hospital volume and patient outcome was found; Negative findings = no relationship or an inverse relationship was found.

For specific mortality outcomes, results of the included studies were reviewed, and key findings were summarised separately. Regarding the mortality outcomes in general, it appears that studies with positive

findings were approximately double the number of ones with negative findings regardless of any adjustment made. However, due to the lack of adequate confounding adjustment, the effect of larger procedure volumes of hospital towards better surgical outcomes may be caused by some external factors which were not captured in the evidence base.

To explore the variation in how mortality results were influenced by different volume cut-offs, a number of box plots (Figure 3 below) were produced to visualise the distribution of higher and lower volume thresholds across studies.

Figure 4 Mortality outcomes against hospital volume upper and lower thresholds

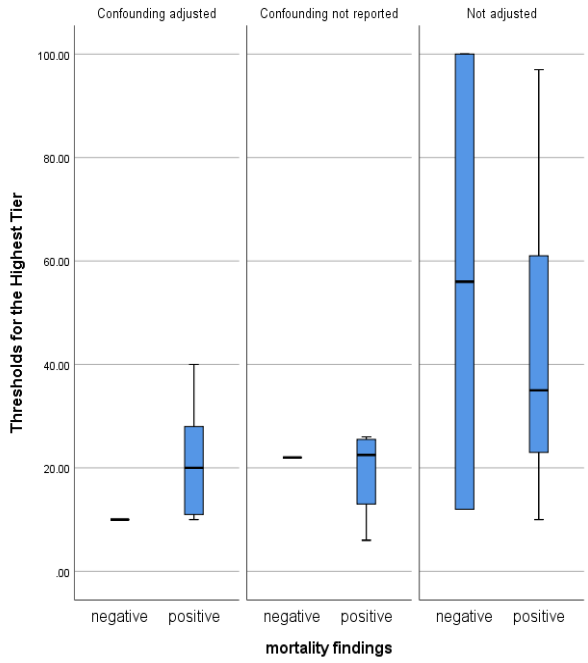


Figure 4A

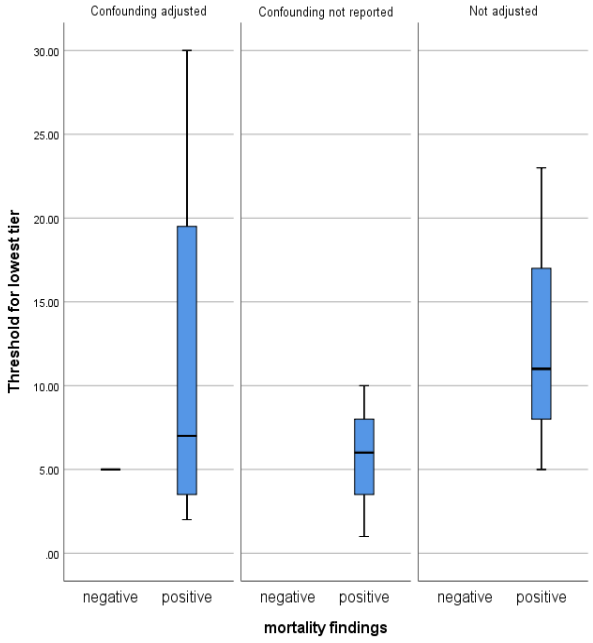


Figure 4B

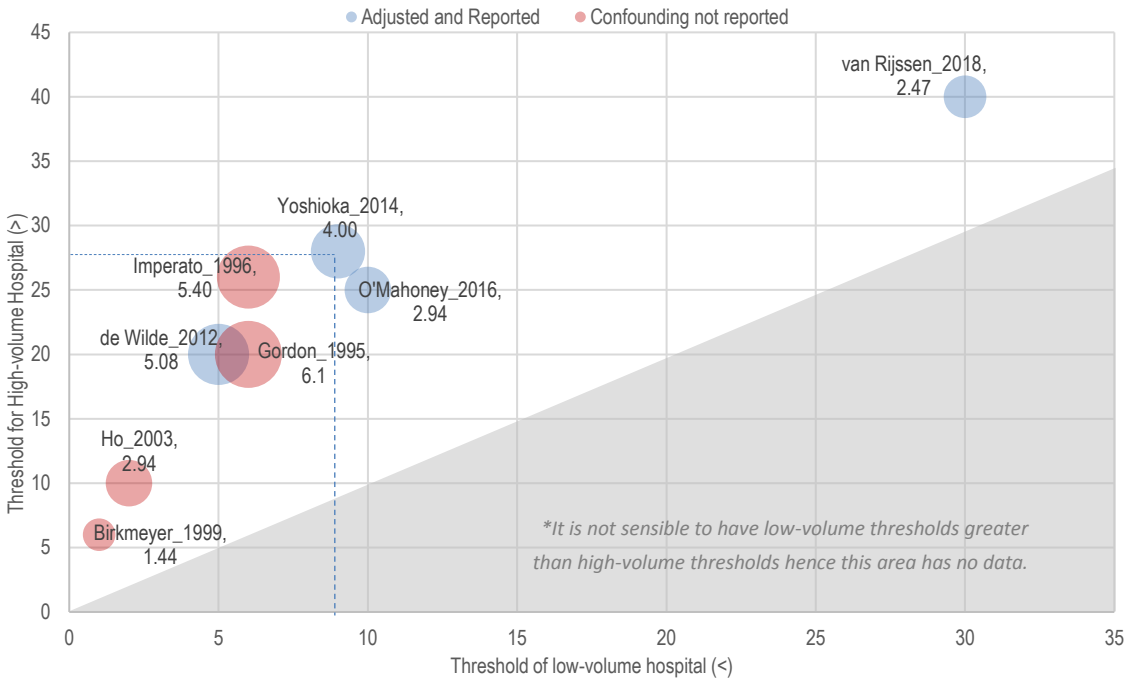
Interpretation Guide: As patient volumes of hospitals were categorised by different cut-offs, only the highest and the lowest cut-offs could be compared across studies. For example, van Rijssen and colleagues[31] grouped hospitals into low-volume (1-20), medium (21-30) and high (31 and above). The number 31 was extracted and compared with other highest cut-offs from other studies (as seen in Figure 4A), whereas the number 20 was used in the same way with lowest cut-offs from other studies (as seen in Figure 4B). Then various cut-offs were plotted in the cluster of whether or not a volume-outcome relationship was identified (positive or negative at the horizontal axis), and whether the studies were adjusted for confounding factors (by plot compartment).

There are no clearly identifiable patterns in this series of box plots, which indicates that the patient volume cut-offs across different hospitals were very diverse in the evidence base. It appears for both high and low-volume cut-offs, studies with positive findings have higher levels of variability. However, due to the imbalance in study numbers in positive and negative findings (as seen in Figure 3), this conclusion may not be reliable. On the other hand, the combination of these two exploratory analyses may also indicate potential publication biases where studies with negative findings may not get published compared to ones with positive findings.

In-hospital mortality

In-hospital mortality was one of the most reported mortality outcomes across all of the included studies. Results were extracted from the studies in detail and presented in Table 10 (Appendix 3). To visualise the impact of hospital volume on in-hospital mortality, the effect sizes of each study represented were plotted against their volume changes in Figure 5. The horizontal and the vertical axis represented the lowest and highest hospital tiers reported in the study respectively. Odd ratios for each study were plotted by different sized circles; the larger the circle the bigger the mortality impact it represents. It is important to note that the size of the impact was relative to each other, which was not in scale to either axis or does not represent any confidence intervals. Also, the overlapping of circles has no statistical meaning. Details of the studies are also described in context for comparative purposes.

Figure 5 In-hospital mortality comparing high-volume to low-volume hospitals



Notes: The studies by Kim et al. and Enomoto et al. were omitted from the plot to improve visualisation. Also, the reference category of different studies was standardised to LVH for better comparison (taking the reciprocals of the ORs).

Interpretation guide: This bubble plot was produced to explore patterns of mortality differences between the high and low hospital procedure volumes across studies. For example, the study by Yoshioka and colleagues (2014),[58] traced by the dotted line, is a confounder-adjusted study, as indicated by the blue icon. It reported a 4-fold mortality increase, as illustrated by the size of blue circle area, when comparing the lowest-volume hospitals (<8/year corresponding to the horizontal axis) to highest-volume hospitals (>28/year to the vertical axis). Hypothetically, a larger volume difference (the north-west quadrant) would associate with larger mortality reduction (by bigger circle areas). However, this was not shown in the plot. In fact, this plot did not show an observable pattern. This implies a substantially heterogeneous evidence base. Although it seems a proportionally large number of studies in the evidence base has found an association between patient volumes and mortality outcome, they were restrained within their own study context which could not be generalised.

After adjusting for confounders, six of the studies incorporated hospital volumes as the predictor for in-hospital mortality.[25,31,58-61] The most recent study by van Rijssen et al.[31] found that hospitals with annual volume less than 30 procedures had over 2.47 times higher mortality rate than hospitals having over 40 per year (95%CI = (1.12, 5.10), p = 0.04). The study published a little earlier by de Wilde and colleagues found an approximately five-fold increase in mortality when comparing high-volume hospitals (HVH) (>20/year) to low-volume hospitals (LVH) (<5/year) (OR = 5.08, 95%CI = (2.84, 9.07), p = NR).[61] In the study by Yoshioka et al.[58] which shared similar hospital volume thresholds with the de Wilde study, VHVH (>28/year) had a comparable reduction in mortality compared to VLVH (<8/year) (OR = 0.25, 95%CI = (0.14, 0.43), p < 0.001), and similar effect sizes were also found when compared to HVH and MVH (OR = 0.53 and 0.61 respectively). With a similar low-volume baseline, Kim and colleagues[60] grouped hospitals into quintiles but with much wider intervals (hence removed as an outlier from the plot). Compared to VLVH (<10/year), VHVH (>215/year) had much higher odds in reducing in-hospital mortality (OR = 0.16, 95%CI = (0.06, 0.41), p < 0.001), and significant mortality reductions were also found in other tiers. A more detailed investigation by Ho and colleagues processed the hospital volumes as a continuous variable (hence not plotted),[25] and found that approximately one procedure increase per year for a hospital could reduce mortality by 6% (OR = 0.94, 95%CI = (0.91, 0.98), p = 0.001). The remaining study by Enomoto et al.[59] combined hospital volumes and surgeon volumes together as a single variable, and the results of this study will be discussed separately in the surgeon-volume section (hence not plotted).

Five studies found the inverse relationship between hospital volumes and in-hospital mortality after Whipple procedures, where co-factors were adjusted but the size of the impact was not reported.[22,55,56,60,61] The study by O'Mahoney and colleagues investigated hospital volume and in-hospital relationships across three states of the USA,[22] and the inverse relationship was found statistically significant and consistent across all of the three states. Studies by Imperato et al. and Gordon et al. compared two regional hospitals to other hospitals in the same state.[55,56] In particular, Gordon and colleagues compared Johns Hopkins hospital (an HVH) to 38 other Maryland hospitals (LVH) and found the mortality was 11.4% higher (adjusted risk difference) and the unadjusted relative risk for postoperative mortality was over 6-fold in LVH hospitals after the Whipple procedure. Imperato and colleagues also found that LVH had over 5-fold of higher mortality than the two regional providers (as HVH). These comparative differences are comparable to the de Wilde and Kim studies, and these four studies appear to have the highest mortality differences among all the included studies.[60,61]

Mortality up to 3 months

Seven studies investigated 30-day mortality, of which four found an inverse association between hospital volume and mortality.[39-42] The study by Kutlu and colleagues not only compared different hospital volumes but also compared different surgical approaches (open versus laparoscopic pancreaticoduodenectomy, OPD and LPD respectively).[39] The study showed that, for both laparoscopic and open approaches, the inverse association between hospital volume and mortality was consistent throughout all scenarios. The most significant differences were observed between the highest (>25/year) and lowest volume hospitals (1-5/year) for both LPD and OPD, with odds ratios of 3.77 and 2.47 respectively. Also, the difference between the 3rd and 4th volume tier was not significant for both approaches (p = 0.48 and p = 0.33 for LPD and OPD respectively).

Lidsky and colleagues also investigated the combined effect on hospital volume and travel distance.[40] The study found that, compared to receiving Whipple procedures in low-volume centres within a short travel distance, the mortality rate was more than 75% lower when patients received the procedure in high-volume centres far away (95%CI = (0.11, 0.53), p < 0.001). The other four studies did not report comparative differences but only the raw mortality rates,[33,34,38,42] and three of them did not find any statistically significant association between hospital volumes and 30-day mortality. [33,34,38] The raw percentages were extracted and provided in Table 8 of Appendix 3.

Seven studies investigated 90-day mortality including the ones authored by Kutlu and Lidsky et al. above.[39,40] The 90-day results from these two studies were very similar to their 30-day findings. When confounding was adjusted, van der Geest and colleagues found that hospitals with procedure volumes lower than 5 per year had a 2.59 times higher odds of mortality compared to hospitals that perform 40 procedures or more.[32] In addition, the study authored by Kagedan and colleagues was the only one on 90-day mortality outcome only,[30] and they found mortality was also significantly elevated in medium (20-40/year) and low-volume hospitals (10-20/year) (OR = 2.47 and 1.92 respectively) compared to HVH (>40/year). However, the study did not provide feasible explanations on reasons why the mortality was even higher in medium volume hospitals than low-volume ones. For 90-day mortality in general, the comparative differences between different volume-tiers were less prominent compared to in-hospital mortality.

Long term survival

Four studies investigated long term survival for patients receiving the Whipple procedure. All four studies found that high hospital volumes had prolonged patient survival.[29,32,42,48] After adjusting for confounding factors, van der Geest and colleagues[32] found that patients had 1.34 times higher hazard of death when receiving a Whipple procedure in a hospital that had a procedure volume of less than 5 per year compared to over 40 per year (95%CI = (1.09, 1.65), p = 0.006). The earlier study by Gooiker et al. (2014)[41] utilised LVH (<10/year) as the reference point and found significant reductions in hazard of death in higher volume hospitals (HR = 0.70 and 0.91 for HVH [>20/year] and MVH [11-19/year] respectively). The other two studies also found similar results; it appears that the long-term survival benefit of high hospital volumes for Whipple surgery was further reduced.

Studies with negative findings

Ten studies did not find hospital volume to be significantly associated with mortality outcomes, and most of them either did not adjust for any confounding factors or did not provide sufficient information on factor adjustment. Four studies[43,45,57,62] had some level of confounding adjustment but there were potential issues around methodologies and factors used in these studies. Although demographic factors were claimed to be adjusted in the study by Nordback et al.,[62] the comparative differences in mortality between dichotomised high and low-volume hospitals were not in line with definitions of hospital tiers (low, medium and high, n = 3). Further, Addeo et al.[43] and Nymo et al.[45] found that hospital volumes were not a predictor for mortality. However, certain factors which were adjusted in the model were identified to be significantly influenced by hospital volumes. In the Addeo study, POPF was further investigated where centre volume was revealed to be

a significant predictor. Similarly, the study by Nymo et al.[45] included relaparotomy as a predictor for 90-day mortality and found hospital volumes were not associated with the mortality outcome. However, this predictor was considered as an outcome later and shown to be significantly associated with hospital volume. This indicates that the volume effect was masked by fistula developments and reoperation, which highlights the importance of factor adjustments in studies. Finally, the study by Zaydfudim and Stukenborg utilised several very advanced statistical models to investigate the association between case-volume and mortality.[57] In all their models, there is no statistically significant association between case-volume for Whipple surgery and patient deaths, where patients' demographic profiles and co-morbidities were significant mortality predictors. Although this study did not have a positive finding, it provided useful insights to inform the essence of the association between hospital volume and patient mortality.

Surgeon volumes and mortality

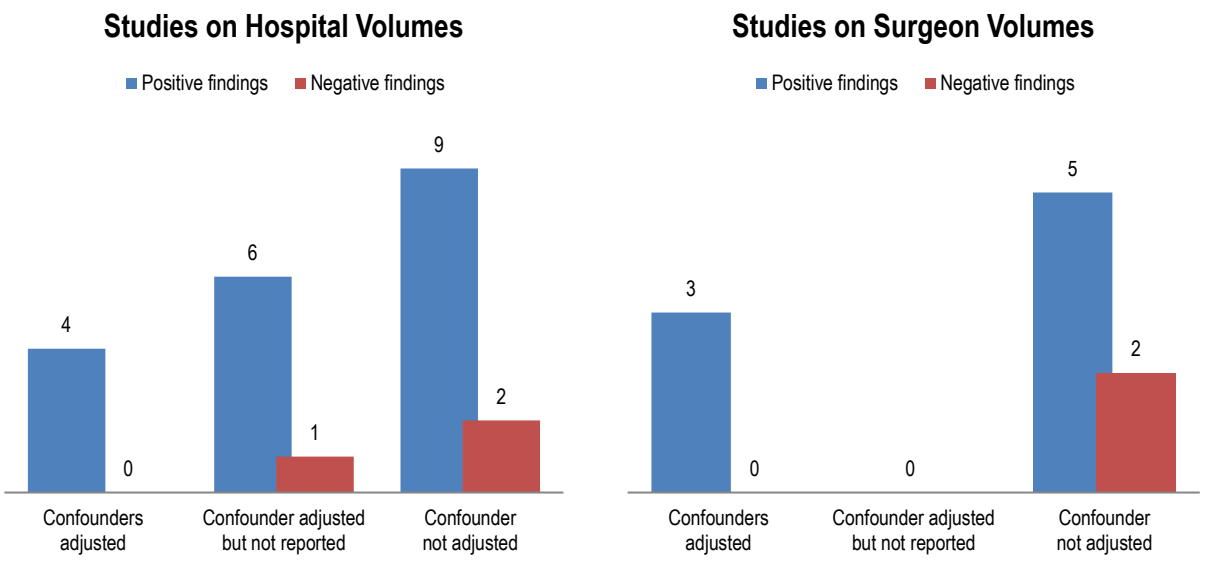
Surgeons' procedure volume was also investigated as a separate factor in 12 studies; most of the studies focused on in-hospital mortality (n = 8), yet for this outcome only half of them (n = 4) adjusted for any confounders,[24,53,59,62] and only two presented their impact.[59,62] Among the eight studies of in-hospital mortality, all except one[62] found an inverse association between surgeon volume and in-hospital death. However, the findings of these studies were still somewhat inconsistent. Ho and colleagues found both surgeon and hospital volumes were independent predictors to the in-hospital mortality (versus low-volume, OR = 0.80 and OR = 0.85 for high-volume surgeons [HVS] and HVH respectively).[24] The most recent study by Schneider et al. also confirmed the significant association between high-volume surgeons and low patient mortality in their study results (versus low-volume surgeon [LVS], OR = 0.56 and OR = 0.46 for MVS and HVS respectively). However, while all other potential confounding factors were controlled for (although effects not reported), it is not clear how hospital volumes could influence in-hospital mortality and how hospital and surgeon volumes would interact. Enomoto and colleagues combined surgeon volume with hospital volume and grouped hospitals into four tiers.[59] Setting the low volume hospital (<11/year) and low surgeon volume (<5/year) as the baseline, the study found that an increase in hospital volume (>11/year) alone could reduce in-hospital mortality (OR = 0.54, 95%CI = (0.33, 0.90), p = 0.018), but surgeon volume increases did not (p = 0.130). When both surgeon and hospital volumes were increased to high tier, in-hospital mortality could be reduced by 68% (OR = 0.32, 95%CI = (0.20, 0.49), p < 0.001). This raised the question of whether or not surgeon volume change alone could be an independent factor in predicting in-hospital mortality.

The rest of the five studies (one[47] also investigated in-hospital mortality) looked at longer-term mortality (30-day, 60 day and 90-day); two found an inverse association while three did not. The studies did not perform any factor adjustment or did not provide sufficient information to show how the adjustment was done. Therefore, the association between surgeon volume and longer-term mortality was uncertain. The reported effect sizes and raw mortality rates were extracted and presented in detail in Table 8 of Appendix 3.

Procedural volumes and patient length of stay (LOS)

The patient LOS after a Whipple procedure was the second most studied outcome in the included studies. The impact of both hospital and surgeon volumes on LOS were studied (n = 27), where 22 studies focused on hospital volume and 10 studies reported surgeon volume (five investigated both). Most of the studies found high hospital and surgeon volumes were associated with a shorter LOS in general, despite the variations on how LOS was defined. However, most of the studies did not have appropriate confounding adjustment; only four studies presented the necessary information for all predictors. The study numbers by each category were plotted in Figure 6 below. It should be noted that there were many variations in how LOS was defined and investigated in the included studies. Detailed discussion was provided in Research Question 1, and these variations may prevent across-study result comparisons.

Figure 6 Confounding adjustment for LOS outcomes, stratified by hospital and surgeon volume



Note: Positive finding = a positive relationship between hospital volume and patient outcome were found; Negative findings = no relationship or an inverse relationship was found.

Hospital volume and LOS

Across the four studies analysing hospital volumes with confounding adjustment, four different types of hospital stay were reported. The total postoperative days (POD) for each patient were analysed in three studies[22,30,53] but all differently depending on the method used. Total PODs were grouped to quartiles by Kagedan and colleagues[30] and rate of patients staying longer than the 3rd quartile (often considered as prolonged stay) were compared against three hospital volume tiers. Compared to HVH (>40/year), patients in LVH (10-19/year) had 1.51 times higher odds (95%CI = (1.19, 1.90), $p < 0.05$) of experiencing a prolonged stay, but not the MVH (20-39/year). However, the cut-off number of days for the fourth quartile (i.e. over 75th percentile) was not reported in the study. Similarly, Schneider and colleagues dichotomised the POD into either below or over 14 days.[53] They found both high (>32/year) and medium (10-31/year) hospitals had a

significantly reduced the rate of prolonged stay over 14 days (OR = 0.73 and OR = 0.88 respectively) versus LVH (1-9/year). This result was similar to the study by O'Mahoney et al.[22] Shi and colleagues[20] treated the POD as a continuous variable, and found that, versus LVH (1-4/year), MVH (5-11/year) can reduce approximately 2.7 PODs and HVH (>12/year) can reduce about 4.2 days. This result is roughly comparable to another study by Lidsky and colleagues.[40] Due to the different approaches used in these studies, it is unclear whether these results are comparable to one another. Lastly, the Enomoto study reported total admission days for Whipple surgery.[59] Again this study explored the compound effect of both hospital and surgeon volume, but the outcome was the number of total admission days (TAD). It appeared when hospital volume was controlled, higher surgeon volume could reduce about 2.44 TADs (95%CI = (-3.59, -1.30), $p < 0.001$). It is unclear whether there is variation in how PODs and TADs are defined. Therefore, it appears studies agreed on the inverse association between hospital volumes and LOS, but it is impossible to compare across-study results due to significant variation in how LOS is analysed and reported. While LOS was investigated, four studies also compared ICU days. They all found high hospital volumes could reduce ICU days but none of the studies adjusted for any confounding. Full details of all studies were extracted and are presented in Table 10 (Appendix 3).

Surgeon volume and LOS

Among the 10 studies on surgeon volumes, only two failed to identify any statistically significant association between higher surgeon volumes and shortened LOS.[35,52] Variations in LOS outcomes were observed, whereby four different types of LOS were specified, while another two studies did not define LOS.[52,62] All three adjusted studies reported an inverse relationship between LOS and surgeon and hospital volumes. With similar effect sizes to hospital volumes, 2.7 PODs were expected to be reduced for patients who had the Whipple surgery done by MVS (5-11/year), and a 4.2-day reduction was associated with HVS (>12/year). While controlled for hospital volumes, increasing surgeon volume by 5 or more could potentially reduce hospital LOS (as TADs) by 2.97 days (95%CI = (-4.42, 1.51), $p < 0.001$).[59] This impact was higher than hospital volume changes as seen above (a 2.44-day reduction). When combining both high-volume surgeon and hospital, the total admission days could be shortened by 5.65 days (95%CI = (-6.70, -4.60), $p < 0.001$). Although LOS was analysed differently, Schneider and colleagues[53] also found surgeon volume increases could have a larger impact in reducing prolonged PODs over 14 days when compared to hospitals. This appeared to be a common finding for LOS outcomes, which is different to what was observed for mortality outcomes.

Other outcomes

Reoperation and readmission were also studied in the evidence base.

Four studies found that higher case volumes were associated with lower reoperation rates, where two of them were on hospital volumes[30,34] and the other two were on surgeon volumes.[21,46] The two surgeon-volume studies did not adjust for any potential confounders whereas both the hospital-volume studies made some adjustments. Where confounding adjustments were not conducted, reoperation rates at different volume tiers were extracted only (including the study by Ansari et al.[34]) due to the Mantel-Haenszel adjustment. Only one study authored by Kagedan and colleagues (2017)[30] reported an odds ratio. The study found that

comparing to high-volume hospitals (>40/year), low-volume hospitals (10 to 20/year) could have 1.73 times more reoperations (95%CI = (1.28, 2.32), $p < 0.05$), and this was the only statistically significant result.

Readmission was also considered as a clinically relevant outcome and investigated in the evidence base. Among the studies investigating readmission after the Whipple procedure, only two studies found that higher hospital volumes were associated with a reduction in 30-day readmission rate (detailed results were extracted in Table 10 of Appendix 3).[28,47] Two studies investigated surgeon-volumes but neither found significant associations.[33,47] Only one study explored the 90-day readmission over the commonly investigated 30-day results but did not find any significant difference by volume.[30]

The overall finding on associations between patient volumes by hospitals or surgeons and reoperation or readmission were inconsistent. The associations between case-volumes and failure of the surgery (as represented by readmission and reoperation) are likely to be uncertain.

Research Question 3

What initiatives have been successful in improving outcomes – internationally and in Australia?

Evidence highlights

Initiatives that improve surgical outcomes for Whipple procedures include:

- the implementation of evidence-based guidelines and standardised care plans;
- board certification of surgeons performing Whipple procedures;
- individual or group partnerships/collaborations between high and low-volume hospitals;
- incorporating expertise from hospitals with proven excellence in Whipple procedures;
- utilising surgical risk calculators or computed tomography (CT) skeletal muscle assessments to determine "at risk/complicated" patients, and transferring them to specialised hospitals.

Summary of results

To address this research question, literature was sourced through targeted, non-systematic searches of peer-reviewed and grey literature. Initiatives aimed to improve outcomes in patients undergoing a Whipple procedure include the development and implementation of evidence-based guidelines on standardised care plans, board certification of surgeons performing Whipple procedures, ongoing partnerships between high and low-volume hospitals, learning expertise from hospitals with proven excellence in the Whipple procedure and use of surgical risk calculators or CT skeletal muscle assessments to determine patients more likely to development complications so they can be transferred to specialised hospitals with the necessary infrastructure to treat them. As noted above, centres that achieve superior surgical outcomes for Whipple procedures are likely to have all factors present at their institution (surgical expertise, optimal care pathways and specialised resources/infrastructure). The absence of one or more of these factors possibly explains the variability seen in surgical outcomes for Whipple procedures among high-volume centres. Thus, in order to achieve optimum surgical outcomes for Whipple procedures, the implementation of several initiatives may be required, depending on the individual hospital and its current resources.

Pitfalls in the volume-outcome relationship

In discussion of Research Questions 1 and 2, the majority of the included studies supported that high-volume hospitals and surgeons were associated with better clinical outcomes for the Whipple procedure. However, there was substantial heterogeneity among the evidence base regarding measures of surgical outcomes and volume thresholds. This problem was amplified by methodological issues exhibited in most studies, making them prone to bias. Further, a limited number of well-performed studies also showed that low-volume hospitals and surgeons are able to deliver outcomes on par with high-volume centres or surgeons. In particular, the effects of volume on mortality and LOS became non-significant when other non-volume factors were fully controlled, or mortality-related risks (e.g. fistula) were considered. This reinforces the notion that procedure volume may not be a reliable measure of quality of care for the Whipple procedure.

Given these caveats, the current evidence base could not be used to support a definitive conclusion that high-volume hospitals or surgeons would result in better surgical outcomes for the Whipple procedure. A view commonly expressed in the literature regarding the volume-outcome relationship is that volume per se does not predict surgical outcomes, rather it is a surrogate for other factors that contribute to better surgical outcomes. Further, some studies suggest that hospital or surgeon volumes are more likely to be influenced by other factors such as local, district or national health policies, hospital staffing and resources, and the baseline population at risk. Procedure volumes are outcomes of these factors instead of causes of different surgical outcomes. Therefore, rather than focussing on the volume-outcome relationship, it might be more prudent to ask the following questions:

1) What are the common patient-, surgeon- and hospital-related features and initiatives across high-volume hospitals?
2) Could they be transferred to low-volume centres to achieve good surgical outcomes for the Whipple procedure?

The two questions above are the interpretation of Research Question 3. To answer this question, additional literature was sourced from targeted, non-systematic searches of peer-reviewed and grey literature. While every effort was made to identify as many initiatives as possible, the initiatives and literature identified in Research Question 3 should not be seen as all-encompassing, rather as a representative sample.

Key relevant initiatives

A number of initiatives were identified, which can be grouped into four categories: patient perspectives, surgeon perspectives, hospital perspectives and governance perspectives. A summary table is presented below to outline the initiatives and the evidence in support.

Table 3 Summary of initiatives implemented to improve surgical outcomes

Initiatives	Evidence summary
Patient perspectives	
Providing evidence-based, personalised surgical plans and perioperative care according to patients' risk profile	Implementing surgical risk calculators can assist in the identification of at-risk patients and lead to alterations in the clinical pathway to optimise their outcome.[69-73]
Surgeon perspectives	
Providing surgical training in both high and low-volume settings with certification programs by expert surgeons	Participation of a board-certified instructor or expert surgeon in Japan led to reductions in mortality, postoperative complications and length of stay following Whipple procedures.[74,75]
Hospital perspectives	
Standardisation and optimisation of postoperative care plans	The use of ERAS was proven effective in reducing complications and avoiding failure-to-rescue for Whipple procedures.[28,76-78]
Support root-cause identification for more specific outcomes other than just mortality	Reducing incidences of failure-to-rescue and allow mortality reduction via early detections and resolutions of severe complications.[26,30-32,39,40,46]
Promote transparent, evidence-based hospital performance benchmarking and indicators	Indicators may include staffing, resources, multidisciplinary-team collaborative work etc.[15,26,30,79,80]

Initiatives	Evidence summary
Partnerships between high-volume (or hospitals with proven excellence in Whipple procedure) and low-volume hospitals	Creating partnerships/collaborations between low and high-volume hospitals can lead to improved post-operative outcomes in the low-volume hospitals.[81]
Clinical governance perspectives	
Clinical quality registries	Clinical quality registries ensure procedures are conducted in accordance with evidence-based guidelines and improve patient outcomes.[82,83]
Clinical capability frameworks	Clinical capability frameworks outline the necessary infrastructure, services and staffing requirements for institutions to conduct Whipple procedures safely.[84]

Abbreviations: **ERAS** = enhanced recovery after surgery.

Personalised care pathways for patients receiving the Whipple procedure

Patient baseline risk plays an important prognostic role for the Whipple procedure. Investigated by both Research Questions 1 and 2, patient demographic profiles and co-morbidities have been shown as significant predictors for the surgical outcomes. For patients with a high baseline risk profile, such as suffering from severe comorbidities, perioperative care tailored to suit an individual patient's needs is necessary to ensure a successful surgical outcome. This could only be achieved by understanding the prognostic risk factors prior to the surgery.

A possible solution may be the use of a surgical risk calculator for the Whipple procedure, or measurement of skeletal muscle volume using computed tomography (CT), to identify those patients at high risk of significant complications. These high-risk patients could then be treated at highly specialised hepatopancreaticobiliary hospitals equipped with the resources deemed necessary for the successful and timely management of significant postoperative complications. This should result in better postoperative outcomes and lower mortality.

Two studies discussing the use of risk calculators for the prediction of postoperative complications after a Whipple procedure were identified in the literature.[69,70] Aoki and colleagues developed a Whipple-specific surgical risk calculator based on data from 17,564 patients in the Japanese National Clinical Database.[69] Anther surgical risk calculator developed by the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is available online.[70] A surgeon or patient may input 21 different postoperative variables plus the Current Procedural Terminology code and receive an estimate risk percentage for 9 different outcomes, as well as a predicted length of stay.[70] A study assessing the effectiveness of the ACS NSQIP for Whipple procedures concluded that the results from the calculator were congruent with the estimates of general surgical complications.[70]

Another tool that has been assessed for its ability to predict surgical outcomes for the Whipple procedure is the assessment of quantitative body composition measurement by CT. Several studies have investigated the relationship between quantitative body composition and various surgical outcomes for Whipple procedures and other types of pancreatic resection.[71-73,85] In three of the studies that investigated survival, low skeletal muscle volume was observed to be significantly associated with poorer results.[71-73] In another study low

skeletal muscle volume was found to be an independent preoperative predictor of infectious complications after Whipple procedures.[85]

Surgical training by expert surgeons

An alternative to an ongoing collaboration between high and low-volume centres is for surgeons to visit and learn best practices from clinical experts from hospitals with proven records of excellence in conducting Whipple procedures. This initiative has been described by Chedid et al. who demonstrated reductions in blood transfusions, greater negative margins and lower perioperative mortality in a low-volume centre following a visit from a high-volume centre surgeon.[74]

In Japan, a board certification system for expert surgeons (hepato-biliary-pancreatic field) has been established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. A review to assess the effectiveness of board certification on outcomes for Whipple procedures was conducted by Miura et al. (2016).[75] They reported that 30-day mortality and operative mortality rates were significantly lower with participation of board-certified instructors or expert surgeons (1.0% and 2.2%) than without (1.7% and 3.8%; both $p<0.001$).[75] In addition, total length of hospital stay was shorter with participation of board-certified instructors or expert surgeons (41.8 days) than in those without (48.1 days, $p<0.001$).[75] In Whipple procedures performed without participation of board-certified instructors or expert surgeons the incidences of reoperation within 30 days, bleeding > 2,000ml, blood transfusion, anastomotic leak, bile leakage, acute renal failure and cardiac event were significantly higher ($p<0.05$). A similar board certification system could be established in Australia to improve surgical outcomes for Whipple procedures.

Standardisation of perioperative care

Enhanced recovery after surgery (ERAS) otherwise known as standardised care pathways, are standardised perioperative care plans aimed to optimise patient surgical outcomes. Three primary studies have shown ERAS for Whipple procedures can decrease patient length of stay without compromising patient outcomes,[76] reducing complications such as delayed gastric emptying,[68] and readmission.[28] A systematic review and meta-analysis encompassing studies from ten countries found that the implementation of ERAS significantly reduced total postoperative days by >4 days (95% CI = (-5.72, -2.61), $p <0.01$), overall morbidity (OR = 0.63, 95% CI = (0.54, 0.74), $p <0.01$) and delayed gastric emptying (OR =0.56, 95%I = (0.44, 0.71), $p <0.01$) compared with conventional perioperative care.[77]

These findings are supported by Satoi et al. who found that institutions which instigated perioperative standardised procedures reported significantly lower incidences of delayed gastric emptying (OR = -0.499, $p=0.008$) and incisional surgical site infections (OR = -0.999, $p <0.001$) compared to non-standardised institutes.[78] Hospital and surgeon volume (low versus high) had no reported effect on the prevalence of these complications. Therefore, the authors concluded that the adoption of a standardised process of care for Whipple procedures at the institutional level, but not hospital/surgeon volumes, may be important in reducing post-Whipple procedure complications.

Focus on causes of mortality – "failure-to-rescue"

Mortality is one of the most important surgical outcomes for the Whipple procedure. In the evidence base of this review, most primary studies explored the impact of different hospital and surgeon volumes against mortality outcomes, especially in-hospital mortality; however, the cause of death was rarely investigated or reported.

Failure-to-rescue, as discussed previously in Research Question 1, is defined as mortality following severe complications.[32] In the context of Whipple procedures these complications may include postoperative pancreatic fistula (POPF, clinical-relevant grades), PPH and delayed gastric emptying. These severe complications were analysed in several studies as additional clinical outcomes together with mortality, but mortality and complications were treated as separate outcomes. Further, seven studies recognised the importance of "failure-to-rescue" as an outcome,[26,30-32,39,40,46] but only one study reported this specific "failure-to-rescue" rate as a composite clinical endpoint.[31]

A recently published study from The Netherlands by van Rijssen and colleagues found that mortality had a weaker association with raw complication rates but had the most significant association with complications when actions to resolve severe complications had failed or been absent.[31] The finding of this study pointed out the pitfall of only focusing on all-cause mortality rather than procedure-specific complications, which highlighted the need for early detection and management of complications after the Whipple procedure. While to prevent complication rates via better perioperative care is equally important, the key to warrant a good surgical outcome for the Whipple procedure is the ability to resolve emerging complications at an early stage to reduce their associated harm.

Therefore, this key initiative is to allow root-cause identification for patient deaths after a Whipple procedure, and to understand how life-threatening complications (or any detrimental postoperative events) could be mitigated or resolved. The study by van Rijssen and colleagues identified a number of measures such as optimising hospital resource allocations, increasing staffing especially around ICU intensivists and interventional radiologists, and multidisciplinary care.[31] These measures would allow concerns or potential complications to be escalated when necessary to manage severe complications at early stage. The realisations of these aspects are commonly observed in high-volume hospitals, but they are not exclusive to high-volume hospitals. In fact, the implementation of these measures should be independent from procedure volumes. They could be considered as key performance indicators for hospitals and assessed against non-volume benchmarks for quality of care.

Utilisation of non-volume key hospital performance indicators

Although the evidence of volume-outcome relationship was heterogeneous across the included studies, one consistent theme was identified from most of studies: high-volume hospitals were more likely to be well equipped and sufficiently staffed to deliver better a surgical outcome for patients receiving Whipple procedures. However, it has not been clear from the evidence base regarding the association between hospital procedure volumes and its resource/staffing levels. A number of studies highlighted that "low-volume" centres, as long as some key performance indicators were satisfactorily met, could deliver good surgical outcomes

(including but not limited to the Whipple procedure) as well.[15,26,30,79,80] Therefore, this initiative is to identify key aspects of hospitals other than caseload which drives a good surgical outcome.

In 2009, Joseph and colleagues explored the pairwise relationships between procedure volumes, system resources and surgical care quality (represented by mortality) for hospitals performing pancreatic resections.[23] The study found that optimised and sufficient system resources are more relevant to better surgical outcomes than procedure volumes, and this finding explains the equivalent or better outcomes seen in low-volume hospitals. Through the literature review, a number of key hospital resource and staffing indicators were identified, including:

- Sufficient levels of staffing especially in ICU
- The availability of interventional radiologists
- Multidisciplinary team consultation

Also, a number of hospital rating schemes and assessment benchmarks, such as HealthGrades and Leapfrog Survey, proposed by entities in both private and public sectors have been made available. Although hospital and surgeon volumes are still considered as a key criterion, a range of resource and staffing related criteria are also considered when hospitals are rated. It should be noted that these rating schemes and criteria are developed and primarily applied in the USA. The applicability of them under the Australian clinical context remains unclear. In summary, hospitals at any volume tiers might be able to use these indicators to assess and improve care provision. Further research may be needed to validate these key indicators, and it would be useful to provide evidence-based benchmarks on these indicators.

Partnerships between hospitals

The development of hospital-level partnerships or collaborations is another initiative which could improve surgical outcomes in patients indicated for Whipple procedures. For example, Ravaioli and colleagues demonstrated a partnership between a low-volume and high-volume hospital could significantly improve pancreas surgery outcomes.[81] The authors suggested the following aspects likely attributed to the improvements in surgical outcomes:

- Patients were preoperatively discussed by high and low-volume surgeons regarding their suitability for surgery via email and telephone, and by multidisciplinary conference calls for more complex cases.
- Patients whose surgery was considered too complex for the low-volume hospital were transferred to the relevant high-volume hospital.
- The high-volume surgeon assisted during the procedure at the low-volume hospital, either as operating surgeon or by assisting the local surgeon.
- Postoperatively, frequent email and telephone contact was maintained between the high and low-volume centre surgeons for patient management, particularly with regard to treatment of complications.

Similar improvements in surgical outcomes of low-volume hospitals performing pancreatic resections as a result of a state-wide collaboration between low and high-volume hospitals (19 academic and community

hospitals) were reported by Healy and colleagues.[86] The authors observed significant improvements in risk-adjusted major complications rates and mortality rates for pancreatectomy between two time periods (2008–2010 and 2011–2013) driven by improvements in low-volume hospitals. They suggested that participating in a regional surgical collaborative may allow low-volume hospitals to achieve short-term outcomes comparable to higher-volume hospitals. Aspects of the state-wide collaboration include regular interactions with other surgeons from whom techniques and procedures can be learned, educational materials and training in health care quality improvement theory and practice.

Clinical quality registries

Clinical quality registries systematically monitor the quality of health care in terms of appropriateness (adherence to guidelines) and effectiveness (patient outcomes)[82] and can improve patient outcomes by reinforcing adherence to guideline-recommended care and identification of preoperative risk factors associated with poor surgical outcomes. Studies have repeatedly demonstrated clinical quality registries improve patient-related outcomes and reduce risk-adjusted mortality.[83] However, there are no clinical quality registries for Whipple procedures in Australia.

Clinical capability frameworks

Clinical capability frameworks outline a service (a surgical or medical procedure) and specify the infrastructure, workforce and support services required to provide it in a safe and effective manner. These processes are designed to ensure patient safety and minimise clinical risk. Most states in Australia have clinical capability frameworks pertinent to Whipple procedures. These frameworks ideally ensure Whipple procedures are only performed at appropriate centres across Australia.

Further, guidelines from The Australian and New Zealand Hepatic, Pancreatic and Biliary Association (ANZHPBA) specifies hospitals undertaking hepatic, pancreatic and biliary surgery should have the following:

1. Infrastructure: an operating theatre with a fully staffed recovery room, intensive care unit and/or a high dependency unit, an endoscopy suite and facilities for advanced laparoscopic surgery.
2. Services: a 24-hour pathology, an inpatient imaging, radiological and oncological services.
3. Staff: ancillary staff (for example, physiotherapist and social worker), surgeons, anaesthetists, nursing and technical staff with a specific interest in HPB surgery, interventional radiologist and back up staff for endoscopy and ultrasound imaging.[84]

Again, implementing these recommendations would likely assist in improving patient-related outcomes.

Research Question 4

What are the likely barriers to implementing a minimum volume framework in Australia and what mitigating factors should be considered?

Evidence highlights

- The volume-outcome relationship is complex and is influenced by patient, provider and hospital factors.
- The implementation of a volume framework would result in the centralisation of services relating to Whipple procedures. Centralisation of services would disproportionally burden rural practices and patients, cause economic disruption and limit the ability of high-volume centres to effectively treat patients while maintaining high-quality care.
- Restricting the framework to metropolitan hospitals will mitigate many of the perceived barriers. Further, implementing a volume framework may improve surgical training and the availability of resources.

Summary of results

To address this research question, literature was sourced from targeted, non-systematic searches of peer-reviewed and grey literature. Studies that identified factors impacting the ability to implement a volume-based framework were included. Each of the included studies was reviewed for relevant themes relating to barriers and mitigating factors (levers) that may influence the ability to implement a volume-based framework. Resources were extracted until no new themes were identified. As such, while every effort was made to identify relevant factors, the references used in Research Question 4 should not be seen as all-encompassing, rather as a representative sample. The combined results of the searches are presented thematically. Several themes regarding levers and barriers for the implementation of a volume-based framework were identified. For example, perceived barriers included the limitation of using volume as a marker of quality, institutional burden, and patient understanding, expectation and burden. By contrast, potential levers included improvements in patient and trainee education and greater access to resources.

Considerations regarding volume

Evidence base

The quality of the studies evaluating the effects of hospital and/or surgeon volume on the outcomes of Whipple procedures is low. The studies are primarily retrospective analyses of hospital records or national registry data (level IV or III-b) with few Australian-based studies. Further, these studies are often confounded as they fail to adjust for patient demographics (or have limited information allowing them to do so), use item codes to identify procedures and lack uniformity regarding the cut offs for low-, medium- and high-volume. High quality trials do not exist and are unlikely to be performed. Therefore, caution must be used when interpreting and extrapolating the results from these studies.

Measuring volume

There are two hypotheses which seek to explain the volume-outcome relationship. The "practice makes perfect" hypothesis suggests surgeons become more proficient in a procedure the more times they perform it. Thus, at higher volume institutions, surgeons have a greater opportunity to practice and potentially produce superior outcomes than at lower volume institutions. The "selective referral" hypothesis suggests institutions with better outcomes attract more patients and thus become high-volume institutions.[87]

However, the effects of volume on the outcomes of Whipple procedures are unlikely to be as simple as this. Volume is a cumulative measure of patient, provider and hospital factors.[88,89] For example, high-volume hospitals are typically large metropolitan hospitals which have greater infrastructure, support services and standardised procedures compared to smaller hospitals. They may also be more proficient at patient selection, anaesthesia and postoperative care. Thus, they are better equipped to manage complex procedures and complications compared to low-volume hospitals.

Applicability of volume

Volume thresholds and the number of patients allocated to each group varied considerably among the included studies. The ability to perform Whipple procedures in each hospital is constrained by the prevalence of the underlying condition(s), the number of patients willing to undergo treatment, and the availability of hospital resources and staff. These variables will differ substantially within and between given regions. Further, rural surgeons often perform procedures at several hospitals. Therefore, the hospital's volume may not necessarily correlate to a low-volume surgeon.[90] These constraints suggest implementing a volume-framework may not be appropriate for many institutions.

Given low-volume institutions can produce comparable outcomes to high-volume institutions,[15,29] it indicates there are several modifiable factors that can improve the quality of care. Therefore, future work should identify quality improvement strategies and specific practices of high-quality institutions and export them to poorer performing centres. This would improve patient-related outcomes independent of procedure volume.[91]

Barriers to implementing a volume-based framework in Australia

Implementing a volume-based framework in Australia is likely to result in centralisation of procedures, staff and resources associated with the Whipple procedure. Smaller, typically regional institutions are likely to be disproportionally affected as they are restricted by the number, type and the location of patients they serve. Consequently, there are a number of barriers that may limit the applicability of implementing a volume-based framework in Australia.

Loss of access to a range of services associated with Whipple procedures

For rural surgeons, restricting the type of services they are able to provide limits their ability to confidently and appropriately manage emergencies, post-surgical complications or undertake related procedures owing to their lack of exposure or detraining.[92-96] The same is likely to apply to associated staff like interventional radiologists, anaesthetists and nurses. If complications do arise, they can be costlier, poorly managed and may

result in poorer outcomes. This may have a follow-on effect. Given rural centres will have fewer complex patients, local practices or hospitals are unlikely to have a sufficient caseload to offer specific training programs to surgeons. Consequently, rural practices are less likely to recruit, retain or train surgeons which further hinders rural and remote medicine.[93,94]

Economic disruption of the market

From an economic perspective, implementing a volume-based framework will increase the market power of high-volume hospitals. This may confer increased contractual power and a diminished incentive to develop risk-adjusted outcome reporting and quality improvement programs.[97] This may additionally impede the ability of new competitors to enter the market place as there is a limited number of patients undergoing Whipple procedures each year.[95] Further, lower volume institutions might be excluded from future competitive bids or may ask for lower amounts in order to "buy market share".[97]

Patient understanding and expectations

There are limited studies evaluating patients' understanding and interpretation of hospital performance in the context of Whipple procedures. In general, patients infrequently seek information relating to hospital performance, and often do not understand or trust the information provided.[98] Rather, patients tend to focus on personal factors such as hospital location rather than quality.[97,99,100] When patients in the USA were informed about the increased risk of performing a procedure at a low-volume institution, they were often willing to accept it in order to stay in their local environment.[101] This represents a substantial issue because patients should ideally select hospitals based on quality not necessarily volume or location.

Patient burden

Implementing a volume-based framework will disproportionally affect rural patients as their proximity to an institution capable of performing the procedure will likely increase. Consequently, patients will have to travel substantial distances in order to receive care – a problem amplified in a country as large as Australia. Furthermore, requiring patients to have their surgery far away from home will reduce the immediate support of family friends, allied health workers and their primary physician. This can contribute to feelings of isolation and reluctance to travel. These effects have significant financial and emotional costs on patients and can result in the delay or avoidance of treatments.[101,102]

It is unclear how patients that require immediate treatment, or are too unstable to transfer to a higher-volume setting, will be treated if volume-based frameworks are implemented.[95]

Hospital burden

Whipple procedures are technically demanding and lengthy. This places considerable burden on operative staff and resources. Consequently, depending on how many institutions are affected (noting in the USA only 10% of institutions met the criteria for "high-volume"[90]), hospitals may be unable to meet the demand for these procedures while maintaining high levels of quality.[95,103] Conceivably, this may not necessarily be a problem for the Whipple procedure, as the procedure is relatively rare. However, it may place an increased

burden on institutions if patients require commonly co-administered interventions such as radiation therapy or chemotherapy.

Levers to implementing a volume-based framework

There are a number of levers which may assist in the implementation of a volume-based framework. For example, improvements in resource allocation, standardisation of procedures and restricting the framework to metropolitan institutions may serve to implement volume-frameworks and promote best practice.

Rural practice

The barriers to implementing a volume-based framework, particularly in a rural setting, can be mitigated if volume requirements are restricted to metropolitan institutions.[104] Thus, rural health care would remain unaffected. However, rural institutions should be informed of factors which contribute to the "volume effect" and try to implement them where applicable.

Access to resources

High-volume institutions typically have greater resources that are associated with improved patient care including nursing staff, ICU and operative guidelines/standardised procedures.[105] High-volume institutions often have access to multidisciplinary teams which assist in optimising patient care and, from a practitioner's perspective, enhance the transfer of knowledge which facilitates greater care in the future.[106] Collectively, these processes enhance patient care and may enable more complex/comorbid patients to be successfully treated.

Guidelines and standardised best practices

During this review, a number of clinical tools aimed at enhancing peri- and postoperative outcomes were identified. The tools primarily focused on patient selection and implementing standardised procedures designed to aid postoperative complication management. Implementing these procedures was associated with improved outcomes following the Whipple procedure.[78,107,108] Given there are no Australian guidelines regarding the Whipple procedure, implementing standardised procedures will likely improve outcomes. Further, by limiting the number of institutions performing the Whipple procedure, it would be relatively easy to implement Australian-wide guidelines or standardised procedures.

Furthermore, by limiting the number of institutions performing the procedure, creating, standardising and maintaining data (or some form or registry) would be easier. This would enable the effects of any policy or procedural alterations to be determined. This is particularly important considering the relatively rarity of the procedure in Australia.

Improvements in surgical training

Teaching institutions offer specific training programs (for example fellowship or residency programs) which result in improved care following a Whipple procedure (decreased LOS, costs and in-hospital mortality[105]). These improvements are attributable to the diverse range of patients that trainees are exposed to, the presence of surgical educators, experienced staff and mentors, the frequency which patients are seen, and

the increased likelihood of having resources, services and technologies which assist with pre-, peri- and postoperative management.

Given, high-volume hospitals are often teaching institutions it is likely that implementing a volume-based framework will improve surgical training as more, potentially diverse patients are funnelled to these institutions.

Clinical quality registries

Clinical quality registries collect, analyse and report on the quality of health care provided at hospitals with the aim to improve patient outcomes.[82] There are several clinical quality registries in Australia which are likely applicable to the Whipple procedure. For example, the Australian and New Zealand Audit of Surgical Mortality, the Victorian Cancer Registry and the Upper Gastrointestinal Cancer Registry.[109-111] As an example, the upper gastrointestinal cancer registry collects clinical and patient information from individuals diagnosed with primary cancer of the pancreas, liver, oesophagus, stomach and biliary system. The registry sends reports to participating hospitals informing how their quality of care compares to other hospitals and where improvement could be made.[111,112] However, creating a nation-wide specific registry for Whipple's or all low-volume procedures would be beneficial to improving healthcare processes as they are often more reliable and informative than information generated by hospital administrative systems,[113,114] could facilitate the transfer of knowledge from high-performing units to lower-performing units and are able to generate early warnings when patient-related outcomes start to worsen. A case study from Western Australia demonstrated the value of clinical quality registers on outcome of Whipple procedures (Box 1).

Box 1 Case study: Practice change in Western Australia

The centralisation of Whipple services in Western Australia serves as an example of how well-designed surgical mortality audits can improve healthcare. The Western Australian Audit of Surgical Mortality (WAASM) identified high mortality rates following a Whipple procedure (approximately 16%). Consequently, Western Australia's Chief Medical Officer and the Department of Health established a working group to discuss how the Whipple procedure services could be improved. The working group established new guidelines recommending that Whipple procedures should be limited to specific hospitals with appropriately trained personnel, infrastructure and multidisciplinary support.[115] Further, the working group proposed restricting the procedure to working hours, ensuring a second qualified surgeon is present for assistance and implementing a credentialing process.[116] The Western Australian Department of Health has since implemented some of the recommendations and have mandated that all Whipple procedures be performed at either the Fiona Stanley Hospital or Sir Charles Gairdner Hospital (comprehensive cancer centres), and have since observed only one death associated with the procedure.[9,115] Collectively, the Western Australian process highlights how using mortality audits to identify high-risk surgeries, utilising working groups to identify areas of improvement and engaging with the Departments of Health to implement these changes can facilitate superior healthcare and patient related outcomes.

Clinical capability framework

Clinical capability frameworks outline the workforce, infrastructure and support services required to perform surgical procedures in a safe and effective manner.[117] Thus, clinical capability frameworks identify where a patient should be treated to ensure optimal results. In Australia, most, if not all states have established clinical capability frameworks. The Queensland and South Australian frameworks outline the requirements for Whipple procedures.[118,119] Whipple procedures are designated surgical complexity V, the highest level of complexity, and as such, the clinical capability framework recommends the procedure should occur at a large metropolitan hospital, with multidisciplinary teams; 24 hour dedicated surgical support.[118,119] There is an opportunity to implement a nation-wide clinical capability framework which would assist standardising the procedural requirements for Whipple procedures to promote safe outcomes.

Board certification

There are no board certification processes for Whipple procedures in Australia. The procedure is taught to general surgery trainees during their surgical education and training.[120] The Australian and New Zealand Hepatic, Pancreatic and Biliary Association (ANZHPBA) offers a further two-year post-fellowship training program designed to improve a surgeon's skill, technique and management of patients undergoing hepatic, pancreatic or biliary-related surgery. The course outline does not specifically address Whipple procedures; however, the ANZHBPA recommends each surgeon undertakes approximately 25 – 30 pancreatic resections throughout the training process.[84] However, owing to the rarity of Whipple procedures, achieving similar volumes may be difficult thus hampering a surgeon's ability to become an expert in this procedure. Therefore, creating a board certification program may assist in training and identifying surgeons who are proficient in the procedure.

Conclusions

There is a substantial body of evidence that has investigated the relationship between procedure volume and patient outcomes for the Whipple procedure. Studies have correlated mortality, LOS, complications, reoperations and readmissions with hospital and surgeon procedure volume; however, there is substantial variation between studies in terms of how these outcomes were defined and measured. In addition, fewer than half of the studies that investigated these outcomes adjusted for confounding factors. Without adjustment for confounding, the true association between procedure volume and patient outcomes cannot be determined. As a result of the variability in the defined outcomes and adjustment of confounding, meta-analysis was not appropriate, and the results were synthesised narratively.

Overall, the literature demonstrated a positive association between higher procedure volume and better patient outcomes; however, the better patient outcomes achieved at high-volume centres or by high-volume surgeons may not be due to volume per se, but as a result of other factors commonly found in high-volume centres or surgeons (i.e. standardised care plans, processes, surgical techniques, and infrastructure). The few studies that appropriately adjusted for potential confounding effects found that better surgical outcomes were driven by factors other than volume. Therefore, the causal relationship between high procedure volume and superior surgical outcome is uncertain for the Whipple procedure. Due to the heterogeneity in the evidence base, no reasonable volume thresholds for conducting Whipple procedures in Australian practice could be identified in the literature.

Initiatives to improve surgical outcomes for Whipple procedures identified in the literature are related to the factors commonly present in high-volume hospitals. These include access to ancillary support services, specialist support to manage complications, optimal care pathways and high surgeon expertise. When all of these factors present at a hospital, which is more likely to be high-volume centre, superior surgical outcomes were often observed. The absence of one or more of these factors may explain the variability seen in surgical outcomes for Whipple procedures among high-volume centres. This may also explain some of the superior surgical outcome for Whipple procedures delivered in low-volume settings when these factors were present. Rather than regarding procedure volume as an independent cause, the volume factor is more likely to be a proxy to reflect the service provision adequacy by hospitals or surgeons. Thus, in order to achieve optimum surgical outcomes for Whipple procedures, the implementation of these initiatives may be required.

The volume-outcome relationship is complex and is influenced by patients, healthcare providers and hospital factors. In Australia, the implementation of a volume framework is likely to result in the centralisation of services for Whipple procedures into high-volume centres. A local case study from Western Australia demonstrated that centralisation of Whipple procedures can result in significant reductions in mortality. With adequate support for hospital staffing and facilities, successful Whipple procedures can be achievable regardless of volume; however, whether this is economically feasible in Australia requires further investigation.

Recommendations

In this review, the Review Working Group (RWG) has been closely involved in providing guidance and clinical inputs to the review outcomes. While significant heterogeneity is noted in the evidence base regarding procedure volume thresholds for hospitals and surgeons, members of RWG agree that a minimum of six Whipple procedures per year for a hospital that is appropriately resourced is more likely to be associated with good surgical outcomes. However, further research is warranted to verify this minimum threshold in the Australian clinical context.

Developed in consultation with the RWG, the following recommendations are suggested to improve the outcomes of Whipple procedures in Australian clinical practice.

Patient perspectives

1. Utilise evidence-based patient risk triaging tools to deliver appropriate care pathways for patients who undergo a Whipple procedure.
2. Provide education to patients to promote better clinical practices.

Surgeon perspectives

3. Provide surgical training on the Whipple procedure in high and low-volume centres by expert surgeons.

Hospital perspectives

4. Promote the standardisation of perioperative care including Enhanced Recovery After Surgery (ERAS).
5. Establish systems, processes and resources for effectively supporting the care of patients undergoing complex surgery including the capacity for identifying and rescuing the deteriorating patient
6. Focus on root-cause identification for adverse outcomes and improving identified system issues.
7. Utilise non-volume key hospital performance indicators.

Clinical governance perspectives

8. In the absence of any agreed minimum volume, all jurisdictions are recommended to implement the WA model of centralisation at designated centres of excellence.
9. Promote high-low-volume hospital partnerships.
10. To establish a high-level guideline to ensure hospitals providing the service have the capability and operate within the Scope of Practice of the organisation.
11. Establish and utilise data from clinical audits and registries at a national level to inform guidelines.

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Appendix 1 Search strategies

Table 4 PubMed search strategy

Search number	Keywords and syntax	Search results
1	(Pancreaticoduodenectomy[MeSH Terms]) OR Pancreaticoduodenectomy[Title/Abstract]	9151
2	(((((Pancreas/surgery[MeSH Terms]) OR Pancreatic Diseases/surgery[MeSH Terms]) OR Pancreatic Neoplasms/surgery[MeSH Terms]) OR Pancreatitis, Chronic/surgery[MeSH Terms]) OR Ampulla of Vater/surgery*[MeSH Terms]) OR Common Bile Duct Neoplasms/surgery[MeSH Terms]	33051
3	(Whipple[Title/Abstract]) AND surg*[Title/Abstract]	991
4	((((Whipple[Title/Abstract]) AND surg*[Title/Abstract])) OR ((((((Pancreas/surgery[MeSH Terms]) OR Pancreatic Diseases/surgery[MeSH Terms]) OR Pancreatic Neoplasms/surgery[MeSH Terms]) OR Pancreatitis, Chronic/surgery[MeSH Terms]) OR Ampulla of Vater/surgery*[MeSH Terms]) OR Common Bile Duct Neoplasms/surgery[MeSH Terms])) OR ((Pancreaticoduodenectomy[MeSH Terms]) OR Pancreaticoduodenectomy[Title/Abstract])	37244
5	(hospital*[Title/Abstract]) OR surgeon*[Title/Abstract]	1285264
6	(((hospital*[Title/Abstract]) OR surgeon*[Title/Abstract])) AND volume[Title/Abstract]	35785
7	(Hospitals, High-Volume[MeSH Terms]) OR Hospitals, Low-Volume[MeSH Terms]	1129
8	("Centralized Hospital Services/statistics and numerical data"[Mesh])	54
9	("Health Facility Size/statistics and numerical data"[Mesh])	1173
10	("Surgicenters/organization and administration"[Mesh])	1341
11	("Surgeons/statistics and numerical data"[Mesh])	502
12	(Surgery Department, Hospital/standards[MeSH Terms]) OR Surgery Department, Hospital/utilization[MeSH Terms]	1048
13	Workload[MeSH Major Topic]	7990
14	(((((((((Hospitals, High-Volume[MeSH Terms]) OR Hospitals, Low-Volume[MeSH Terms])) OR (("Health Facility Size/statistics and numerical data"[Mesh]))) OR (("Surgicenters/organization and administration"[Mesh]))) OR (("Surgeons/statistics and numerical data"[Mesh]))) OR ((Surgery Department, Hospital/standards[MeSH Terms]) OR Surgery Department, Hospital/utilization[MeSH Terms])) OR Workload[MeSH Major Topic]) OR (("Centralized Hospital Services/statistics and numerical data"[Mesh]))) OR ((((hospital*[Title/Abstract]) OR surgeon*[Title/Abstract])) AND volume[Title/Abstract])	47575
15	((((((((((Hospitals, High-Volume[MeSH Terms]) OR Hospitals, Low-Volume[MeSH Terms])) OR (("Health Facility Size/statistics and numerical data"[Mesh]))) OR (("Surgicenters/organization and administration"[Mesh]))) OR (("Surgeons/statistics and numerical data"[Mesh]))) OR ((Surgery Department, Hospital/standards[MeSH Terms]) OR Surgery Department, Hospital/utilization[MeSH Terms])) OR Workload[MeSH Major Topic]) OR (("Centralized Hospital Services/statistics and numerical data"[Mesh]))) OR ((((hospital*[Title/Abstract]) OR surgeon*[Title/Abstract])) AND volume[Title/Abstract]))) AND (((((Whipple[Title/Abstract]) AND surg*[Title/Abstract])) OR ((((((Pancreas/surgery[MeSH Terms]) OR Pancreatic Diseases/surgery[MeSH Terms]) OR Pancreatic Neoplasms/surgery[MeSH Terms]) OR Pancreatitis, Chronic/surgery[MeSH Terms]) OR Ampulla of Vater/surgery*[MeSH Terms]) OR Common Bile Duct Neoplasms/surgery[MeSH Terms])) OR ((Pancreaticoduodenectomy[MeSH Terms]) OR Pancreaticoduodenectomy[Title/Abstract]))	588
Total: 588 hits		

Table 5 Embase search strategy

Search number	Keywords and syntax	Search results
1	'pancreaticoduodenectomy'/de OR pancreaticoduodenectomy	18873
2	chronic AND ('pancreatitis'/de OR pancreatitis)	32691
3	'surgery'/exp OR 'surgery'	6006731
4	#2 AND #3	15437
5	pancreatic AND ('neoplasms'/exp OR neoplasms)	116616
6	#3 AND #5	64680
7	'pancreas disease'/exp OR 'pancreas disease'	305208
8	#3 AND #7	124301
9	'pancreas cancer'/exp OR 'pancreas cancer'	89051
10	#3 AND #9	42320
11	'vater papilla carcinoma'/exp OR 'vater papilla carcinoma'	2065
12	#3 AND #11	1630
13	'bile duct tumor'/exp OR 'bile duct tumor'	31802
14	#3 AND #13	19696
15	#1 OR #4 OR #6 OR #8 OR #10 OR #12 OR #14	156277
16	'hospital volume'/exp OR 'hospital volume'	2360
17	'surgeon volume'/exp OR 'surgeon volume'	1096
18	'hospital management'/mj	35926
19	('health care facility'/exp OR 'health care facility') AND ('size'/exp OR 'size')	52396
20	('hospital department'/exp OR 'hospital department') AND ('surgery'/exp OR 'surgery')	19116
21	('workload'/exp OR 'workload') AND ('surgery'/exp OR 'surgery')	6757
22	('high-volume surgeon'/exp OR 'high-volume surgeon') AND ('high-volume hospital'/exp OR 'high-volume hospital')	33
23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	116348
24	#15 AND #23	2035
25	#15 AND #23 AND ([article]/lim OR [article in press]/lim OR [editorial]/lim OR [review]/lim)	703
Total: 703 hits		

Table 6 The Cochrane Library search strategy

Search number	Keywords and syntax	Search results
1	MeSH descriptor: [Pancreaticoduodenectomy] explode all trees	225
2	MeSH descriptor: [Pancreatic Diseases] explode all trees and with qualifier(s): [surgery - SU]	426
3	MeSH descriptor: [Pancreatic Neoplasms] explode all trees and with qualifier(s): [surgery - SU]	255
4	MeSH descriptor: [Common Bile Duct] explode all trees and with qualifier(s): [surgery - SU]	97
5	MeSH descriptor: [Ampulla of Vater] explode all trees and with qualifier(s): [surgery - SU]	48

6	MeSH descriptor: [Pancreas] explode all trees and with qualifier(s): [surgery - SU]	155
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	658
8	MeSH descriptor: [Hospitals, High-Volume] explode all trees	7
9	MeSH descriptor: [Hospitals, Low-Volume] explode all trees	3
10	MeSH descriptor: [Hospitals] in all MeSH products	3297
11	MeSH descriptor: [Health Facility Size] explode all trees and with qualifier(s): [standards - ST, statistics & numerical data - SN]	5
12	MeSH descriptor: [Surgeons] explode all trees and with qualifier(s): [statistics & numerical data - SN]	7
13	MeSH descriptor: [Surgery Department, Hospital] explode all trees and with qualifier(s): [utilization - UT, standards - ST]	2
14	MeSH descriptor: [Surgicenters] explode all trees and with qualifier(s): [statistics & numerical data - SN, organization & administration	1
15	MeSH descriptor: [Workload] explode all trees	352
16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	3641
17	#7 AND #16	3
Total: 3 hits		

Table 7 Clinical practice guideline and grey literature resources

Institution	Website
National Institute of Clinical Excellence (NICE)	www.nice.org.uk
Scottish Intercollegiate Guidelines Network (SIGN)	www.sign.ac.uk
American Cancer Society	https://www.cancer.org/
Pancreatic Cancer Action Network	https://www.pancan.org/
Agency for Healthcare Research and Quality	https://www.guideline.gov
American College of Gastroenterology	https://gi.org/
American Gastroenterological Association	https://www.gastro.org/
American Pancreatic Association	https://www.american-pancreatic-association.org/
European Society for Medical Oncology (ESMO)	https://www.esmo.org/
European Neuroendocrine Tumor Society	https://nanets.net/
British Society for Neuroendocrinology	https://www.neuroendo.org.uk/
Endocrine Society of Australia	https://www.endocrinesociety.org.au/
Carcinoid-Neuroendocrine Tumour Society Canada	https://cnetscanada.org/
UK & Ireland Neuroendocrine Tumour Society	https://www.ukinets.org/
Japanese Pancreatic Society	http://www.suizou.org/english/index.htm
Japanese Society of Gastroenterology	http://www.jsge.or.jp/english/
Guidelines International Network	www.g-i-n.net

Appendix 2 Search results

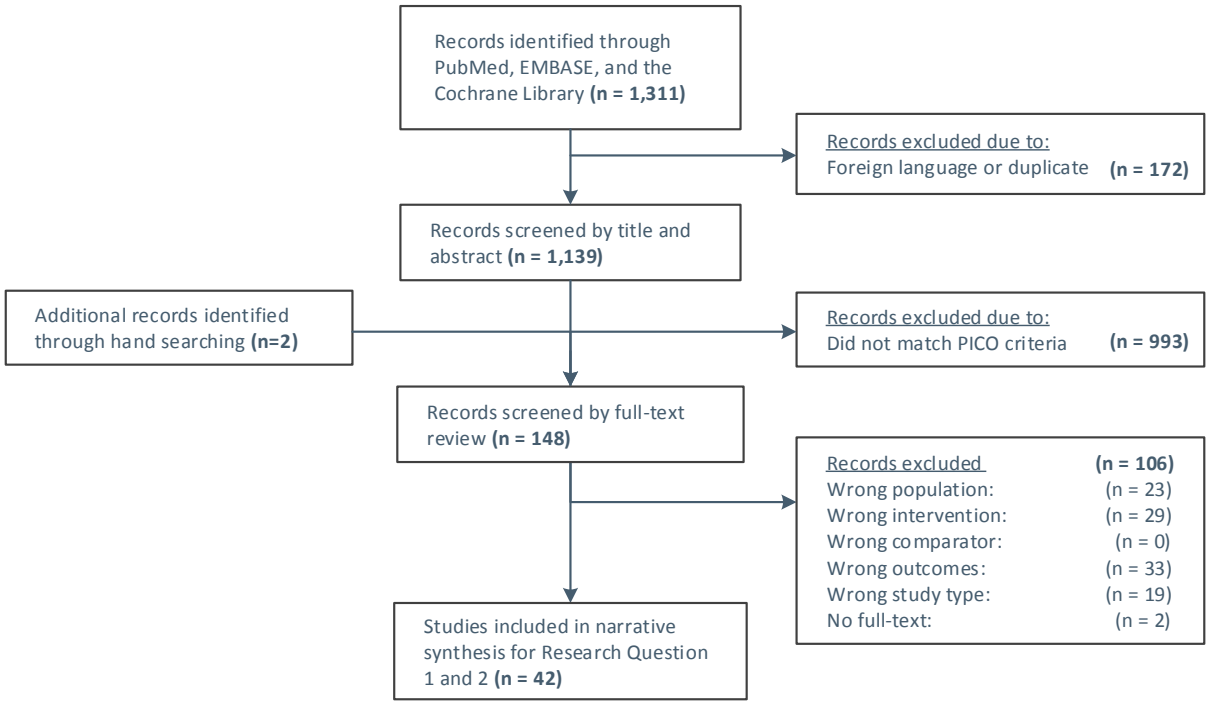
CPGs

In total, 28 CPGS were identified through the literature searches; however, none were relevant to the research questions relating to the volume-outcome relationship for Whipple procedures.

Peer-reviewed literature results

A PRISMA flow chart for the systematic peer-reviewed literature search is presented in Figure 7.

Figure 7 PRISMA flow chart of study inclusion



Appendix 3 Study review and extraction

Table 8 Study profiles and outcomes investigated

Author Year	Country	Database investigated	Total # of Patients	Total # of Hospitals	Years of the case reviewed	Procedure investigated	Volume units and thresholds (per year if no otherwise specified)	Outcome studied					
								Mortality	LOS	Major complication	Pancreatic Fistula	Other procedure related	Others
Nymo et al. 2018 [45]	Norway	National Patient Registry	930	5	2012 - 2016	PD	Q1=513, Q=197, Q=136, Q4=84	90D	TAD	NR	NR	NR	Reoperation
van Rijssen et al. 2018 [31]	The Netherlands	Dutch Pancreatic Audit	1,342	18	2014 - 2015	PD NOS	Q1=20-30, Q2=30-39, Q3(HVH)=40+, @HV	IH (as FTR)	NR	Major: CD-Score=III+	ISPGS-POPF & CR-POPF (Grade B, C)	DGE, PPH (ISPGS), BL	Note: FTR = IH when CDS>3
Kutlu et al. 2018 [39]	USA	National Cancer Database	4,739	587	2010 - 2011	PD: Open = 90.9%, LSPD = 9.1%	Q1=1-5, Q2=6-13, Q3=14-25, Q4=25+, @HV	30D, 90D	NR	NR	NR	NR	Rate of margin positivity
Zaydfudim and Stukenborg 2017 [57]	USA	Heathcare Cost and Utilisation Project 2012 National Inpatient Sample	8,260	432	2012	PD NOS	N/A, case-volumes as continuous variable, @HV	IH	NR	NR	NR	NR	NR
Stella et al. 2017 [26]	Italy	Case Records of Patients from 2 Italian Hospitals	98	2	2004 - 2014	PD NOS	LVH=3, HVH=100	NOS (within the study period)	POD	CD-Score & Major: CD-Score=III+	ISGPF-POPF	NR	Reoperation
Stauffer et al. 2017 [46]	USA	Case Records of Pancreatic Surgery at the Mayo Clinic, Florida	454	1	2005 - 2015	PD & PPPD, data NR	LVS=12-, HVS=12+	90D	NR	Major: CD-Score=III+	ISPGF-POPF	DGE, PPH (ISPGS), SSI	Reoperation
Lidsky et al. 2017 [40]	USA	National Cancer Database	7,086	NR	1998 - 2012	PD & PPPD, data NR	Travel distance and volume combined: ST/LV=(>6.3mile)& (<3.3PD); LT/HV=(97.3mile)& (>16)	30D, 90D	IPD	NR	NR	NR	Readmission
Kagedan et al. 2017 [30]	Canada	Canadian Institute for Health Administration Discharge Abstract Database	2,563	~11	2005 - 2013	PD NOS	LVH=10-19, MVH=20-39, HVH=40+	90D	POD (binary, ± 75 percentile)	NR	NR	NR	ADI, reintubation, reoperation, readmission (90days), cardiac resuscitation
Adam et al. 2017 [54]	USA	Healthcare Utilization Project National Inpatient Sample Data Sets	865	229	2000 - 2012	MIPD (LSPD & robotic)	LVH=22-, HVH=22+	IH	NOS	Overall complication	POPF-NOS	DGE (ISPGS), SSI, frequency, others	NR
Wood et al. 2016 [27]	USA	The State of Florida Agency for Healthcare Administration database	939	6	2010 - 2012	PD NOS	LVH=12-, HVH=12+	IH	POD	NR	NR	NR	NR

Author Year	Country	Database investigated	Total # of Patients	Total # of Hospitals	Years of the case reviewed	Procedure investigated	Volume units and thresholds (per year if no otherwise specified)	Outcome studied					
								Mortality	LOS	Major complication	Pancreatic Fistula	Other procedure related	Others
van der Geest 2016 [32]	Netherlands	Netherlands Cancer Registry	3,420	63	2005 - 2013	PD & PPPD, data NR	Q1=5-, Q2=5-19, Q3=20-39, Q4=40+, @HV	90D, survival	NR	NR	NR	NR	FTR (not defined)
Toomey et al. 2016 [33]	USA	Hospital Database (maybe Florida Hospital, Tampa)	100	2	2012 - 2013	PD NOS	LVH=12-, HVH=12+	30D	NOS, ICU	NR	NR	NR	Readmission (30D)
Shah et al. 2016 [21]	India	Hospital Database (Department of Surgical Gastroenterology, Sher-I-Kashmir Institute of Medical Sciences, Kashmir)	200	1	2002 - 2013	PD NOS	VLVH=1-22, LVH=23-35, MVH=37-56, HVH=58-90, VHVH=97-200	IH	POD	Major: CD-Score=III+	ISGPS-POPF (grades)	DGE, PPH, BL (ISGPS), SSI	Reoperation
O'Mahoney et al. 2016 [22]	USA	New York State State-wide Planning and Research Cooperative System databases; California and Florida state inpatient databases	29,337	NR	2002 - 2011	PD: LVH=70%, MVH=27.3%, HVH=2.9% PPPD: LVH=30%, MVH=72.7%, HVH=92.1%	LVH=10-,MVH=10-24, HVH=25+	IH	14D+/-	NR	NR	NR	Readmission (30D), (other broad categories)
Sutton et al. 2015 [28]	USA	The University Health System Consortium Clinical Database-Resource Manager	9,805	124 - 129	2009 - 2011	PD NOS	LVH=10-, MVH=11-25, HVH=25-60, VHVH=61+	IH	ICU, POD	NR	NR	NR	Readmission (30D),
Ryan et al. 2015 [49]	USA	State of Florida Agency for Healthcare Administration	3,531	NR	1992 - 1994 2001 - 2003 2010 - 2012	PD NOS	Q1=1-3, Q2=4-9, Q3=10-18, Q4=19-36, Q5=36+, @SV/36mo	IH	POD	NR	NR	NR	NR
Yoshioka et al. 2014 [58]	Japan	Japanese Diagnosis Procedure Combination database	10,652	848	2007 - 2010	PD & PPPD, data NR	VLVH=8-, LVH=9-11, MVH=12-17, HVH=18-28, VH=28+ @HV	IH	POD	NR	NR	NR	NR
Shi et al. 2014 [20]	Taiwan	Taiwan Bureau of National Health Insurance	4,038	NR	1998 - 2009	PD NOS	LVH=1-8; MVH=9-24; HVH=25+ LVS=1-4, MVS=5-11, HVS=12+	NR	NOS	NR	NR	NR	NR
Gooiker et al. 2014 [41]	The Netherlands	Netherlands Cancer Registry	1,465	94	2000 - 2009	PD & PPPD, data NR	LVH=10-, MVH=10-19, HVH=20+	30D, 90D, 1Yr, 2Yr	NR	NR	NR	NR	NR
Enomoto et al. 2014 [59]	USA	Healthcare Cost and Utilization Project National Inpatient Sample	3,290	NR	2004 - 2008	PD NOS	LVH=11-, HVH=11+ LVS=5-, HVS=5+	IH	TAD	NR	NR	NR	NR
Ansari et al. 2014 [34]	Sweden	Skåne University Hospital Database	221	1	2000 - 2012	PD NOS	LVH=10-, MVH=10-24, HVH=25+	IH or 30D	POD	Major: CD-Score=III+	ISGPS-POPF	DGE, PPH (ISGPF)	Infections

Author Year	Country	Database investigated	Total # of Patients	Total # of Hospitals	Years of the case reviewed	Procedure investigated	Volume units and thresholds (per year if no otherwise specified)	Outcome studied					
								Mortality	LOS	Major complication	Pancreatic Fistula	Other procedure related	Others
Addeo et al. 2014 [43]	France	Not used	1,325	37	2004-2009	PPPD=12%, PJ = 55%, PG = 42%, Lymphadenectomy = 22%, NOS=2% double check this	LVH=10-, MVH=10-19, HVH=20+	60D	NR	Major: CD-Score=IIIb+	ISGPS-POPF (B,C) = CR-POPF	NR	NR
Schneider et al. 2013 [53]	USA	Healthcare Cost and Utilization Project National Inpatient Sample	25,464	506	2003 - 2009	PD NOS	LVH=1-9, MVH=10-31, HVH=32+ LVS=1-4, MVS=5-15, HVS=16+	IH	14D+/-	NR	NR	NR	Readmission (30D), reoperation, infection, VTE
Hyder et al. 2013 [47]	USA	Medicare data - Surveillance, Epidemiology, and End Result	1,488	298	1998 - 2005	PD NOS	VLVH=1-4, LVH=5-12, MVH=13-24, HVH=35-53 VLVS=1-2, LVS=3-6, MVS=7-20, HVS=21-84	IH, 90D, Readmission	Admission LOS and readmission LOS	NR	NR	NR	Readmission (30D)
Pecorelli et al. 2012 [35]	Italy	Hospital Pancreatic Surgery Database	610	1	2001 - 2009	PD NOS	LVS=12-, HVS=12+	30D	POD	NR	ISGPS-POPF	DGE (other definition)	NR
Kim et al. 2012 [60]	Korea	Health Insurance Review and Assessment Service	4,975	126	2005 - 2008	double check this	VLVH=10-, LVH=10-18, MVH=19-35, HVH=54-111, VHVH=215+	IH	NR	NR	NR	NR	NR
de Wilde et al. 2012 [61]	Netherlands	Nationwide Registry: KiwaPrismant	2,155	56	2004 - 2009	PD NOS	VLVH=5-, LVH=5-10, MVH=11-19, HVH=20+	IH	NR	NR	NR	NR	NR
Schmidt et al. 2010 [36]	USA	Indiana University Hospital Clinical Database	1,003	1	1980 - 2007	PD NOS	LVS=20-, HVS=20+	IH or 30D	NR	NR	ISGPS-POPF	NR	NR
Kennedy et al. 2010 [44]	USA	Providence Portland Health System Database	94	1	2005 - 2008	PD NOS	LVS=10-, HVS=10+	60D	POD	Major: CD-Score=III+	NR	NR	NR
Schell et al. 2008 [29]	USA	Five Hospital Database Moffit-Long Hospital, Veterans Affairs Medical Center of San Francisco, Mount Zion Hospital, San Francisco County General Hospital	369	4	1989 - 2003	PD: LVH=43.9%, HVH=35.3% PPPD: LVH=56.1%, HVH=64.1%	LVH=1, HVH=23	30D, (survival) 3Yr, 5Yr	ICU, POD	NR	POPF-NOS	DGE, PPH (NOS)	Blood loss, SSI, reoperation
Rosemurgy et al. 2008 [51]	USA	Florida Agency for Health Care Administration	2,012	NR	1995 - 1997 2003 - 2005	PD NOS	Q1=1-3, Q2=4-9, Q3=10-16, Q4=17+, @SV/33mo	IH	IHD	NR	NR	NR	NR
Pal et al. 2008 [37]	UK	Dr Foster® (Register for all NHS Hospitals in England)	3,378	1999 - 2002, 101 2002 - 2005, 73	1999 - 2005	PD NOS	Q1=1-43, Q2=46-77, Q3=81-144, Q4=173-317, @HV/7yrs	30D	NR	NR	NR	NR	NR
Topal et al. 2007 [50]	Belgium	National Medical Registry data	1,794	126	2000 - 2004	PD NOS	LVH=10-, HVH=10+	IH	POD	NR	NR	NR	NR

Author Year	Country	Database investigated	Total # of Patients	Total # of Hospitals	Years of the case reviewed	Procedure investigated	Volume units and thresholds (per year if no otherwise specified)	Outcome studied					
								Mortality	LOS	Major complication	Pancreatic Fistula	Other procedure related	Others
Ho et al. 2006 [24]	USA	Florida, New Jersey, and New York Hospital Discharge Abstract Files,	8,253	NR	1988 - 2000 (3 periods)	PD NOS	Both surgeons and hospital volume NR	IH	NR	NR	NR	NR	NR
Urbach et al. 2003 [121]	Canada	Canadian Institute for Health Information and the Ontario Registered Persons Database	686	49	1994 - 1999	PD NOS	Q1=2.8, Q2=5.4, Q3=11.4, Q4(HVH)=24.8, @HV	30D	NR	NR	NR	NR	NR
Ho et al. 2003 [25]	USA	State-wide Hospital Discharge Claims	6,652	500	1988 - 1998	PD NOS	Q1=1, Q2=2-3, Q3=4-9, Q4=10+, @HV	IH	NR	NR	NR	NR	NR
Nordback et al. 2002 [62]	Finland	National Hospital Discharge Database (contains details of public and private hospitals in Finland)	350	33, also 98 surgeons	1990 - 1994	PD=270 PPPD=76 DPPD=4	LVH=5-, MVH=5-10, HVH=10+ LVS=1-,MVS=1-3, HVS=3+	IH	NOS	Uncomplicated recovery	NR	NR	Reoperation
Rosemurgy et al. 2000 [52]	USA	State of Florida Agency for Health Care Administration	698	282 surgeons	1995 - 1997	PD NOS	Q1=1, Q2=2, Q3=3, Q4=4-6, Q5=7-9, Q6=10-16, Q7=17+, @SV/33mo	IH	NOS	NR	NR	NR	NR
Birkmeyer et al. 1999 [42]	USA	Health Care Financing Administration's 100% MEDPAR file	7,229	1772	1992 - 1995	PD NOS	VLH=1-; LVH=1-2, MVH=2-5, HVH=5+	IH & 30D	NOS	NR	NR	NR	NR
Birkmeyer et al. 1999 [48]	USA	Health Care Financing Administration's 100% MEDPAR file	7,229	1772	1992 - 1995	PD NOS	VLH=1-; LVH=1-2, MVH=2-5, HVH=5+	Survival	NR	NR	NR	NR	NR
Imperato et al. 1996 [56]	USA	Medicare Claims in New York State	579	117	1991 - 1994	PD NOS	Q1=1-5, Q2=6-10, Q3=11-15, Q4=16-20, Q5=21-25, Q6(HVH)=26+, @HV	IH	NOS	NR	NR	NR	NR
Gordon et al. 1995 [55]	USA	Maryland Health Services Cost Review Commission	501	39	1988 - 1993	PD NOS	Q1=1-5, Q2=6-10, Q3=11-15, Q4=16-20, Q5(HVH)=20+, @HV	IH	ICU, POD	NR	NR	NR	NR

Abbreviations: **ADI** = abdominal drain inserted, **aLOS** = aggregated length of stay, **BL** = bile leak, **CD** = Clavien-Dindo classification, **CR** = clinically-relevant, **D** = day, **DGE** = delayed gastric emptying, **DPPD** = duodenum preserving pancreaticoduodenectomy, **FTR** = failure to rescue, **HV** = hospital volume, **HVH** = high-volume hospital, **HVS** = high-volume surgeon, **ICU** = intensive care unit, **IH** = in-hospital, **IPD** = inpatient days, **ISPGS** = international study group, **LSPD** = laparoscopic pancreaticoduodenectomy, **LT/HV** = long travel/high-volume, **LVH** = low-volume hospital, **LVS** = low-volume surgeon, **MIPD** = minimally invasive pancreaticoduodenectomy, **MVH** = medium volume hospital, **MVS** = medium volume surgeon, **N/A** = not applicable, **NHS** = national health service, **NOS** = not otherwise specified, **NR**= not reported, **PD** = pancreaticoduodenectomy, **PG** = pancreaticogastrostomy, **PJ** = pancreatojejunostomy, **POD** = postoperative days, **POPF** = postoperative pancreatic fistula, **PPH** = post-pancreaticoduodenectomy haemorrhage, **PPPD** = pylorus-preserving pancreaticoduodenectomy, **Q** = quartile, **SSI** = surgical site infection, **ST/LV** = short travel/low-volume, **SV** = surgeon volume, **TAD** = total admission days, **USA** = United States of America, **VHVH** = very high-volume hospital, **VHVS** = very high-volume surgeon, **VLVH** = very low-volume hospital, **VLVS** = very low-volume surgeon, **VTE** = venous thromboembolism.

Table 9 Confounding adjustment performed in the included studies

Author Year	Age	Gender	Comorbidity	If Cancer, location, stage, metastasis	Histopathological diagnosis	Teaching hospital status	Insurance Status	Others
Nymo et al. 2018 [45]	MORTALITY (90D): vs. <65 OR (65-74) = 5.0, 95%CI = (1.6, 22.0), OR (>75) = 13.8, 95%CI = (4.2, 63.0) Overall model p < 0.001 REOPERATION: adjusted, NS	MORTALITY (90D): vs. female OR (male) = 3.4, 95%CI = (1.5, 9.0), Overall model p < 0.001 REOPERATION, vs. female OR (male) = 1.9, 95%CI = (1.3, 2.9), p = 0.001	ALL OUTCOMES: not adjusted baseline reported but not compared	NR	NR	NR	NR	MORTALITY (90D): Reoperation (re-laparotomy) within 30-day, significant.
van Rijssen et al. 2018 [31]	FTR: unit increase, OR = 1.06, 95%CI = (1.03,1.11), p = 0.001	FTR: vs. female, OR=2.10, 95%CI = (1.10, 3.98), p = 0.02	FTR: as ECOG vs. 1, NS	TNM in baseline, NS	FTR: vs. PC, OR (periampullary) = 2.29, 95%CI = (1.18, 4.49), p = 0.02; OR(other) =NS	NS	NR	BMI = NS
Kutlu et al. 2018 [39]	MORTALITY (30D, 90D), MARGIN(+): adjusted, ES not reported	MORTALITY (30D, 90D), MARGIN(+): adjusted, ES not reported	MORTALITY (30D, 90D), MARGIN(+): adjusted, ES not reported	MORTALITY (30D, 90D), MARGIN(+): adjusted, ES not reported	NR	MORTALITY (30D, 90D), MARGIN(+): adjusted, ES not reported		Chemo/radio adjuvant adjusted, ES not reported
Zaydfudim and Stukenborg 2017 [57]	MORTALITY: 10yrs increase (via HGLM) OR = 3.09, 95%CI = (2.41, 3.96), p < 0.001	NR	MORTALITY: 11 comorbidities, all significant	MORTALITY: metastasis = NS	NR	NR	NR	NR
Stella et al. 2017 [26]	not adjusted baseline NS	not adjusted baseline NS	As ASA, not adjusted baseline NS	NR	not adjusted baseline sig. diff.	NR	NR	NR
Stauffer et al. 2017 [46]	not adjusted baseline NS	not adjusted baseline NS	Hypertension, diabetes, ASA, not adjusted baseline sig. diff	NR	NR	NR	NR	BMI = NS
Lidsky et al. 2017 [40]	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted for stages, ES not reported	NR	NR	ALL OUTCOMES: adjusted, ES not reported	NR
Kagedan et al. 2017 [30]	90D MORTALITY: vs.<60, OR (61-70) = 2.51, 95%CI = (1.38, 4.56), OR (71-80) = 3.90, 95%CI = (2.18, 6.98), OR (80+) = 5.52, 95%CI = (2.54, 11.98) PROLONGED LOS: vs. <60 OR (61-70) = 1.65, 95%CI = 1.30, 2.10), OR (71-80) = 2.27, 95%CI = (1.77, 2.90), OR (80+) = 2.72, 95%CI = (1.80, 4.10) REOPERATION, reintubation, ADI also significant	90D MORTALITY: vs.<male, OR= 0.56, 95%CI = (0.38, 0.84), PROLONGED LOS: NS REOPERATION, REINTUBATION: also significant	90D MORTALITY: vs. ACG=0-9, NS PROLONGED LOS: vs. ACG=0-9 OR = 1.35, 95%CI = (1.10, 1.65) 90D READMISSION: vs. ACG=0-9 OR = 1.56, 95%CI = (1.28, 1.90)	PROLONGED LOS: vs. not >14D OR = 0.72, 95%CI = (0.58, 0.90)	NR	NR	NR	SES significant at some level for some outcomes

Author Year	Age	Gender	Comorbidity	If Cancer, location, stage, metastasis	Histopathological diagnosis	Teaching hospital status	Insurance Status	Others
Adam et al. 2017 [54]	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	NR	ALL OUTCOMES: adjusted, ES not reported	not adjusted baseline sig. diff.	not adjusted baseline NS	ALL OUTCOMES: adjusted for race and year, ES not reported
Wood et al. 2016 [27]	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data	NR		not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data
van der Geest 2016 [32]	90D MORTALITY: vs. <65 OR (65-74) =2.14, 95%CI = (1.56 - 2.93), p < 0.001 OR (≥75) = 3.17, 95%CI = (2.23 - 4.52), p < 0.001 OVERALL SURVIVAL: vs. <65 HR (65-74) = 1.16, 95%CI = (1.06 - 1.27), p < 0.001 HR (≥75) = 1.31, 95%CI = (1.16 - 1.47), p < 0.001	90D MORTALITY: vs. male OR = 0.69, 95%CI(0.53, 0.90), p = 0.006 OVERALL SURVIVAL not adjusted baseline NS	NR	90D MORTALITY: *Tumour invasion, vs. T1-2, T3-4=NS OR (Tx) = 3.47, 95%CI = (1.34, 8.98), p = 0.010 OVERALL SURVIVAL: *Tumour invasion, vs. T1-2 HR (T3-4) = 1.20, 95%CI = (1.09, 1.32), p < 0.001 TX = NS *Lymph node status, vs. N0-X HR (N1) = 1.92, 95%CI = (1.75, 2.11), p < 0.001 *Tumour grade vs. Moderate/well diff HR (Poorly)= 1.52, 95%CI = (1.39, 1.66), p < 0.001 Unknown=NS	OVERALL SURVIVAL: location, vs. pancreas HR (Periampullary) = 0.6, 95%CI = (0.55, 0.66), p <0.001	NR	NR	90D MORTALITY: adjusted for time period, NS OVERALL SURVIVAL: adjusted for time period (NS), chemo (sig.) radical resection (sig.) , LN examined (sig.)
Toomey et al. 2016 [33]	not adjusted baseline NS	not adjusted baseline NS	As ASA score not adjusted baseline sig. diff.	not adjusted baseline: TNM = NS AJCC = sig malignancy = sig	not adjusted baseline counts only	NR	NR	NR
Shah et al. 2016 [21]	not adjusted baseline NS	not adjusted baseline NS	not adjusted baseline NS	not adjusted baseline counts only	not adjusted baseline counts only	NR	NR	NR
O'Mahoney et al. 2016 [22]	ALL OUTCOMES: adjusted for race, surgery year, ES not reported	ALL OUTCOMES: adjusted for race, surgery year, ES not reported	ALL OUTCOMES: adjusted for race, surgery year, ES not reported	ALL OUTCOMES: adjusted for race, surgery year, ES not reported	NR	NR	New York, p = 0.44 California, p < 0.63 Florida, p = 0.01 Categories were medicaid, medicare, commercial, other	ALL OUTCOMES: adjusted for race, surgery year, ES not reported
Sutton et al. 2015 [28]	(readmission only) unclear, maybe adjusted baseline NS	(readmission only) unclear, maybe adjusted baseline NS	(readmission only) unclear, maybe adjusted as severity of illness baseline sig. diff.	NR	NR	NR	(readmission only) unclear, maybe adjusted baseline sig. diff.	(readmission only) unclear, maybe adjusted for SES baseline sig. diff.

Author Year	Age	Gender	Comorbidity	If Cancer, location, stage, metastasis	Histopathological diagnosis	Teaching hospital status	Insurance Status	Others
Ryan et al. 2015 [49]	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data	not adjusted no baseline data
Yoshioka et al. 2014 [58]	IH MORTALITY: vs. <60 OR (60-69) = 1.94, 95%CI = (1.30, 2.87), p = 0.001 OR (70-79) = 2.75, 95%CI = (1.86, 4.01), p < 0.001 OR (≥80) = 4·15, 95%CI = (2.61, 6.58), p < 0.001	IH MORTALITY: vs. male OR = 0.48, 95%CI (0.38, 0.62), p < 0.001	IH MORTALITY: vs. CCI=0-2 OR(3), OR(4)= NS OR(5+) = 2.55, 95%CI = (1.85, 3.50), p < 0.05	NR	NR	IH MORTALITY: vs. academic, OR (none) = 1.03, 95% CI = (0.72, 1.47), p = 0.869	NR	NR
Shi et al. 2014 [20]	LOS: unit increase, beta = 0.6, p < 0.001 COST: unit increase, beta = 2.0, p < 0.001, both 95%CI not reported	LOS: vs. female beta=-0.7, p<0.001	LOS: unit increase, beta=-1.0, p<0.001	LOS: vs. ampullary OR (pancreatic) = -1.0, p< 0.001 OR (hepatobiliary) = 0.1, p = 0.287 OR (duodenal) = -1.1, p < 0.001	NR	NR	NR	NR
Gooiker et al. 2014 [41]	SURVIVAL (COX): vs. 50-64 HR (<50) = 0.91, 95%CI = (0.67, 1.24), p = 0.550 HR (65-79) = 1.29, 95%CI = (1.10, 1.52), p = 0.002 HR (80+) = 1.26, 95%CI = (0.801, 1.99), p = 0.326	SURVIVAL (COX): adjusted, NS	NR	SURVIVAL (COX): *__Tumour__, vs. T3, HR (T4) = NS HR (T1-2) = 0.80, 95%CI = (0.68, 0.94), p = 0.007 *__Node__, vs. N1, HR (N0) = 0.68, 95%CI = (0.57, 0.80), p < 0.001 HR (Nx) = 0.12, 95%CI = (0.46, 0.76), p < 0.001 *__Adjuvant Chemo__, vs. No HR (Yes) = 0.59, 95%CI = (0.46, 0.76), p < 0.001	NR	NR	NR	adjusted for period of diagnosis, NS
Enomoto et al. 2014 [59]	IH MORTALITY: vs. 18-55 OR (56-65) & OR(66-75) = NS OR (76+) = 2.76, 95%CI = (1.41, 5.37), p = 0.003 LOS: vs. 18-55 OR (56-65) = NS OR (66-75) = 1.54, 95%CI = (0.13, 2.95), p = 0.032 OR (76+) = 2.85, 95%CI = (-1.21, 4.50), p = 0.001 COST: vs.18-55 OR (56-65), OR(66-75) = NS OR (76+) = 5630, 95%CI = (774, 10,486), p = 0.02	IH MORTALITY: adjusted, NS LOS: adjusted, NS COST: vs. male OR = -3406, 95%CI = (-5656, -1156), p = 0.003	IH MORTALITY: vs. no comorbidity OR (CHF) = 3.35, 95%CI = (1.84, 6.08), p < 0.001 LOS: vs. no comorbidity beta (CHF) = 2.93, 95%CI = (0.38, 5.47), p = 0.024 beta (diabetes) = -1.67, 95%CI = (-2.53, -0.82), p < 0.001	NR	NR	mortality, adjusted, NS	mortality, adjusted vs. Medicare, NS	NR

Author Year	Age	Gender	Comorbidity	If Cancer, location, stage, metastasis	Histopathological diagnosis	Teaching hospital status	Insurance Status	Others
Ansari et al. 2014 [34]	adjusted by MH-ChiSq test variables not specified baseline NS	adjusted by MH-ChiSq test variables not specified baseline NS	as ASA score adjusted by MH-ChiSq test variables not specified baseline NS	NR	Not adjusted overall counts and % reported	NR	NR	NR
Addeo et al. 2014 [43]	DGE: adjusted vs. <70 RR (>70) = 1.62, 95%CI = (1.17, 2.23), p = 0.0031 ALL OTHER OUTCOMES: not adjusted, univariate p>0.15	MORBIDITY: vs. female RR = 1.50, 95%CI = (1.19, 1.90), p = 0.0009 MORTALITY: adjusted, NS DIGESTIVE HAEMORRHAGE, adjusted, NS ALL OTHER OUTCOMES not adjusted, univariate. p>0.15	**as ASA score** MORTALITY: vs. I/II RR (III/IV) = 3.33, 95%CI = (1.61, 6.90), p < 0.001 ALL OTHER OUTCOMES: not adjusted, univariate p>0.15 **as diabetes** FISTULA DEVELOPMENT: vs. present RR (absent) = 2.64, 95%CI = (1.43, 4.78), p = 0.0014	NR	NR	NR	NR	DGE: adjusted for surgical approach (vs. PPPD), sig. also fistula as a sig., risk factor for MORTALITY, HAEMORRHAGE AND DGE.
Schneider et al. 2013 [53]	LOS>14: vs. <65 RR (65-74) = 1.12, 95%CI = (1.04, 1.21), p = 0.005; RR (≥75) = 1.21, 95%CI = (1.11, 1.31), p < 0.001 MORTALITY: not adjusted, baseline NS	LOS>14: adjusted NS	LOS>14: adjusted NS	NR	NR	LOS>14: vs. non-teaching RR (teaching) = 1.10, 95%CI = (1.03, 1.18), p = 0.006, MORTALITY: not adjusted, baseline NS	LOS>14: vs. private RR (Government) = 1.13, 95%CI = (1.05, 1.22), p = 0.02 RR (Self-pay/other) = 1.22, 95%CI = (1.09, 1.35), p < 0.001 MORTALITY: not adjusted, baseline NS	LOS>14: adjusted for race (vs. white), sig. except Asian/Pacific adjusted for region, sig.
Hyder et al. 2013 [47]	READMISSION adjusted, NS	READMISSION adjusted, NS	READMISSION: vs. Comorbidity score<13 OR = 2.06, 95%CI = (1.56, 2.71), p < 0.001	NR	Readmission: adjusted, NS	NR	NR	READMISSION also adjusted for race, LOS (as risk factor), period, income, geographic area, all NS
Pecorelli et al. 2012 [35]	ALL OTHER OUTCOMES: not adjusted, baseline NS POPF: adjusted, ES not reported	ALL OTHER OUTCOMES: not adjusted, baseline NS POPF: adjusted, ES not reported	ALL OTHER OUTCOMES: not adjusted, baseline NS POPF: adjusted, ES not reported	NR	ALL OTHER OUTCOMES: not adjusted, baseline NS POPF: adjusted, ES not reported	NR	NR	POPF: sig. additional risk factors included Wirsung duct diameters, Op time, transfusion, pancreas softness
Kim et al. 2012 [60]	MORTALITY: unit increase OR = 1.04, 95%CI = (1.02, 1.06), p < 0.001	MORTALITY: adjusted, NS	MORTALITY: not adjusted baseline NS	NR	MORTALITY: adjusted, NS	NR	MORTALITY: adjusted, NS	MORTALITY: adjusted for surgical techniques, vs. classical, OR (PPPD) = 0.64, 95%CI = (0.43, 0.96), p = 0.025
de Wilde et al. 2012 [61]	MORTALITY: 10yr increase OR = 1.79, 95%CI = (1.48, 2.16), p < 0.001	MORTALITY: adjusted, NS	NR	NR	NR	NR	NR	MORTALITY: adjusted for calendar year, NS

Author Year	Age	Gender	Comorbidity	If Cancer, location, stage, metastasis	Histopathological diagnosis	Teaching hospital status	Insurance Status	Others
Schmidt et al. 2010 [36]	ALL OUTCOMES: not adjusted, baseline not compared by volume	ALL OUTCOMES: not adjusted, baseline not compared by volume	NR	ALL OUTCOMES: not adjusted, baseline not compared by volume	ALL OUTCOMES: not adjusted, baseline not compared by volume	NR	NR	ALL OUTCOMES: not adjusted, baseline not compared by volume
Kennedy et al. 2010 [44]	MORTALITY: adjusted, ES not reported	MORTALITY: adjusted, ES not reported	**as ASA** MORTALITY: adjusted, ES not reported	NR	MORTALITY: adjusted, ES not reported	NR	NR	NR
Schell et al. 2008 [29]	ALL OUTCOMES: not adjusted, baseline NS	ALL OUTCOMES: not adjusted, baseline sig. diff.	ALL OUTCOMES: not adjusted, baseline NS	NR	ALL OUTCOMES: not adjusted, baseline NS	NR	NR	ALL OUTCOMES: not adjusted, baseline sig. for race
Rosemurgy et al. 2008 [51]	ALL OUTCOMES: not adjusted, baseline not compared by volume	ALL OUTCOMES: not adjusted, baseline not compared by volume	ALL OUTCOMES: not adjusted, baseline not compared by volume	NR	NR	NR	NR	NR
Pal et al. 2008 [37]	ALL OUTCOMES: not adjusted, baseline NR	ALL OUTCOMES: not adjusted, baseline NR	ALL OUTCOMES: not adjusted, baseline NR	ALL OUTCOMES: not adjusted, baseline NR	ALL OUTCOMES: not adjusted, baseline NR	NR	NR	NR
Topal et al. 2007 [50]	MORTALITY: not adjusted, baseline NR	MORTALITY: not adjusted, baseline NR	MORTALITY: not adjusted, baseline NR	NR	NR	NR	NR	NR
Ho et al. 2006 [24]	MORTALITY: adjusted, ES not reported	MORTALITY: adjusted, ES not reported	MORTALITY: adjusted, ES not reported	MORTALITY, : adjusted, ES not reported	NR	NR	MORTALITY: adjusted, ES not reported	MORTALITY: adjusted for race, emergency, geographic locations, ES not reported
Urbach et al. 2003 [121]	MORTALITY: adjusted, ES not reported	MORTALITY: adjusted, ES not reported	MORTALITY: adjusted, ES not reported	NR	NR	NR	NR	NR
Ho et al. 2003 [25]	MORTALITY: adjusted, vs. <60 OR (60-69) = 1.86, 95%CI = (1.40, 2.47), p < 0.001 OR (70-79) = 3.42, 95%CI = (2.61, 4.50) , p < 0.001 OR (80+) = 4.76, 95%CI = (3.41, 6.66), p < 0.001	MORTALITY: adjusted, NS	MORTALITY: vs. no-comorbidity, OR (COPD) = 1.5, 95%CI = (1.15, 1.96) OR (diabetes, mild/moderate) = 0.54, 95%CI = (0.40, 0.74) OR (kidney) = 14.17, 95%CI = (7.15, 28.08) OR (liver mild) = 2.43, 95%CI = (1.31, 4.50) OR (liver moderate/severe) = 4.84, 95%CI = (2.40, 9.75) others including diabetes (w/complication), Peripheral vascular disease, MI and rheumatologic, NS	NR	NR	NR	NR	NR
Nordback et al. 2002 [62]	MORTALITY: adjusted, vs. >61yrs OR = 0.94, 95%CI = (0.91, 0.98), p = 0.004	MORTALITY: not adjusted, baseline NR	MORTALITY: not adjusted, baseline NS	PDAC = 163	MORTALITY: not adjusted, baseline NS	NR	NR	MORTALITY: not adjusted for stent, not adjusted for technique both baseline NS

Author Year	Age	Gender	Comorbidity	If Cancer, location, stage, metastasis	Histopathological diagnosis	Teaching hospital status	Insurance Status	Others
Rosemurgy et al. 2000 [52]	ALL OUTCOMES: unclear, no baseline data	ALL OUTCOMES: unclear, no baseline data	ALL OUTCOMES: unclear, no baseline data	ALL OUTCOMES: unclear, no baseline data	ALL OUTCOMES: unclear, no baseline data	NR	NR	NR
Birkmeyer et al. 1999 [42]	ALL OUTCOMES: adjusted, NS	ALL OUTCOMES: adjusted, NS	ALL OUTCOMES: adjusted, NS	NR	ALL OUTCOMES: adjusted, NS	NR	ALL OUTCOMES: adjusted, NS	ALL OUTCOMES: adjusted for residence locations, NS
Birkmeyer et al. 1999 [48]	SURVIVAL: vs. 65-69 HR (70-74) = 1.20, 95%CI = (1.10, 1.31) HR (75+) = 1.15, 95%CI = (1.06, 1.26)	SURVIVAL: vs. male HR = 1.03 95%CI = (0.96, 1.11)	SURVIVAL: vs. comorbidity<1 HR(>2) = 1.86, 95%CI = (1.73, 2.00)	SURVIVAL: surgical indications, vs. benign pancreatic disease HR (non-pancreatic cancer) = 2.43, 95%CI = (2.05, 2.90) HR (pancreatic cancer) = 5.23, 95%CI = (4.42, 6.17)	NR	NR	NR	SURVIVAL: adjusted for residence location, vs. inside referral region HR (outside) = 0.87, 95%CI = (0.81, 0.95)
Imperato et al. 1996 [56]	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	NR	NR	NR	NR	ALL OUTCOMES: adjusted for admission types, ES not reported
Gordon et al. 1995 [55]	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	ALL OUTCOMES: adjusted, ES not reported	NR	NR	NR	ALL OUTCOMES: adjusted for source of payment, ES not reported	ALL OUTCOMES: adjusted for race, ES not reported

Abbreviations: **95%CI** = 95% confidence interval, **ACG** =adjusted clinical group, **ADI** = abdominal drain inserted, **AJCC** = American joint committee on cancer, **ASA** = American society of Anaesthesiologist score, **BMI** = body mass index, **Chemo** = chemotherapy, **CHF** = congestive heart failure, **COPD** = chronic obstructive pulmonary disease, **D** = day, **DGE** = delayed gastric emptying, **ECOG** = eastern cooperative oncology group, **ES** = effect size, **FTR** = failure to rescue, **HGLM** = hierarchical generalised linear model, **HR** = hazard ratio, **IH** = in hospital, **LN** = lymph nodes; **LOS** = Length of stay, **MH-ChiSq** = Mantel-Haenszel chi squared test, **MI** = myocardial infarction, **N0** = No regional lymph node metastasis, **Nx** = lymph nodes cannot be assessed, **NS** = not significant, **NR** = not reported, **Op time** = operative time, **OR** = odds ratio, **PC** = pancreatic cancer; **PDAC** = pancreatic ductal adenocarcinoma, **POPF** = postoperative pancreatic fistula, **PPPD** = pylorus-preserving pancreaticoduodenectomy, **radio** = radiation therapy, **RR** = relative risk, **SES** = socioeconomic status, **Sig** = significant, **w/complication** = with complications, **Vs** = versus, **Yr** = year.

Notes: Tumour stage has been classified according to TNM system;

Table 10 Results reported in the included studies

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Nymo et al. 2018 [45]	**90D*** vs. Q1 p = 0.56 OR (Q2) = 0.7 95% CI = (0.3 – 1.8) OR (Q3) = 1.7 95%CI (0.6 – 4.2) OR (Q4) = 0 95%CI = (0.0 – 0.4)	**TAD (within 30-day)** (median IQR) Q1 = 13 (9 – 19) Q2 = 17 (12 – 23) Q3 = 16 (12 – 22) Q4 = 15 (10 – 21) P < 0.001	NR	NR	NR	**Reoperation*** vs. Q1 p = 0.034 OR (Q2) = 1.5 95% CI = (0.9 – 2.4) OR (Q3) = 0.7 95%CI (0.4 – 1.3) OR (Q4) = 1.8 95%CI = (1.0 – 3.3)	NR
van Rijssen et al. 2018 [31]	**IH*** vs. ≥ 40/yr OR (30-39/yr) =1.70, 95%CI = (0.84, 3.51), p = 0.14 OR (<30yr) = 2.47, 95%CI = (1.12, 5.10), p = 0.04	NR	**CD>III** Q4-Q1 = 40%	NR	NR	(Only compared between surgical approaches, hence not extracted)	NR
Kutlu et al. (2018)[39]	(for brevity all p values were omitted) **30D* LPD** vs. 4th OR(1st) = 3.772, 95% = (1.006, 9.147), OR(2nd) = 1.781, 95%CI = (1.053, 3.012), OR(3rd) = 1.688, 95%CI = (0.400, 7.116), **30D***, **OPD**, vs. 4th OR(1st) = 2.465, 95% = (1.556, 3.904), OR(2nd) = 1.626, 95%CI = (1.005, 2.738), OR(3rd) = 1.323, 95%CI = (0.752, 2.327), **30D***, vs. OPD OR(LPD) = 1.556, 95%CI = (0.92, 2.624), **90D***, **LPD**, vs. 4th OR(1st) = 3.772, 95% = (1.006, 9.147), OR(2nd) = 1.781, 95%CI = (1.053, 3.012), OR(3rd) = 1.688, 95%CI = (0.400, 7.116), **90D***, **OPD**, vs. 4th OR(1st) = 1.450, 95% = (1.080, 1.946), OR(2nd) = 1.335, 95%CI = (1.009, 1.836), OR(3rd) = 0.870, 95%CI = (0.613, 1.235), **90D***, vs. OPD OR(LPD) = 1.195, 95%CI = (0.852, 1.676),	NR	NR	NR	NR	NR	NR
Zaydfundim et al. (2017)[57]	**IH*,** 5-procedure increment OR = 0.98, 95%CI = (0.83, 1.17), p = 0.858 10- and 50-increments are also available median dichotomisation, vs. each other OR(<M) = 1.32, 95%CI = (0.12, 14.06), p = 0.815 OR(>M) = 0.75, 95%CI = (0.07, 7.99), p = 0.815 non-linear model also NS	NR	NR	NR	NR	NR	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Stella et al. 2017 [26]	**IH** HVH = 2/54 (4%), LVH = 3/44 (7%), p =0.654 HVH = 2/54 (4%), LVH-1st = 0/22 (0), LVH- 2nd, p = 1.000 (HVH vs. LVH-2nd)	**POD** HVH = 17.5±12.9; LVH = 17.1±9.9 p = 0.875	**CD Scores** CD = 1-2 HVH = 24/54 (67%) LVH = 17/44 (61%) CD = 3-5 HVH = 12/54 (33%) LVH = 11/44 (39%) p = 0.793 CD score specific p = 0.902	**ISGPF-POPF** rate HVH = 16/54 (30%), LVH = 12/44 (27%) p = 0.826 grade also available, p = 0.393	NR	**Reoperation** HVH = 6/54 (11%), LVH = 2/44 (4%), p = 0.290	NR
Stauffer et al. 2017 [46]	**90D** LVS = 6/79 (7.6%), HVS = 11/375 (2.9%), p = 0.093	NR	**CD>III** LVS = 31/79 (39.2%), HVS = 58/375 (15.5%) p = 0.001	**ISGPF-POPF** LVS = 16/79 (20.3%), HVS = 43/375 (14.1%), p = 0.043	**DGE** LVS = 16/79 (20.3), HVS = 34/375 (9.1), p = 0.009 **SSI** LVS = 21/79 (26.6%), HVS = 36/375 (9.6%), p = 0.001	**Reoperation** LVS = 10/79 (12.7%), HVS = 17/375 (4.5%), p = 0.015	NR
Lidsky et al. 2017 [40]	**30D***, vs. ST/LVH OR (LT/HVH) = 0.24, 95%CI = (0.11, 0.53), p <0.001 **90D***, vs. ST/LVH OR (LT/HVH) = 0.51, 95%CI = (0.31, 0.83), p = 0.006 **survival***, vs. ST/LVH HR (LT/HVH) = 0.75, 95%CI = (0.63, 0.90), p = 0.002	**IPD*** vs. ST/LVH beta (LT/HV) = -2.0, 95%CI = -(2.42, -1.57), p = <0.001	NR	NR	NR	**Readmission*** vs. ST/LV OR (LT/HV) = 1.07, 95%CI = (0.72, 1.60), p = 0.73	NR
Kagedan et al. 2017 [30]	**90D*** vs. HVH OR (MVH) = 2.47, 95%CI = (1.54, 3.96) OR (LVH) = 1.92, 95%CI = (1.12, 3.27) p = NR	**Prolonged POD(75%+)*** vs. HVH OR (MVH) = 0.90, 95%CI = (0.73, 1.13) OR (LVH) = 1.51, 95%CI = (1.19, 1.90)	NR	NR	NR	**Reoperation*** vs. HVH OR (MVH) = 1.02 95%CI = (0.76, 1.37) OR (LVH) = 1.73 95%CI = (1.28, 2.32) **90D-Readmission*** vs. HVH OR (MVH) = 1.02, 95%CI = (0.82, 1.26), OR (LVH) = 1.04, 95%CI = (0.82, 1.33)	NR
Adam et al. 2017 [54]	**IH** LVH = 28/717 (3.9%) HVH = < 10 (NR) p = 0.34	**NOS*** vs. HVH beta (LVH) = 0.18 95%CI = (-0.03, 0.44), p = 0.09	**(complication occurrence)*** vs. HVH OR (LVH) = 1.68, 95%CI = (1.03, 2.94), p = 0.04	**ISGPF-NOS** HVH = 85/717 (11.8%) LVH = <10 (NR) p = 0.04	**DGE**: LVH = 55/717 (7.7%) HVH = <10 (NR) p = 0.03 **SSI** LVH = 99/717 (13.8%) HVH = 20/148 (13.5) p = 0.99	**Reoperation** LVH = 16/717 (6.2) HVH = <10 (NR) 0.76	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Wood et al. 2016 [27]	**IH** LVS = 10/939 (1%) HVS = 25/939 (3%) p = 0.5452	**POD** (median, mean ± SD) HVS = 11, 14 ± 11.5 LVS = 10, 15 ± 11.9 p = 0.5749	NR	NR	NR	NR	NR
van der Geest 2016 [32]	**90D***, vs. ≥ 40/yr OR (<5) = 2.59 95%CI = (1.32, 5.09), p = 0.006 OR (5-19) = 2.11 95%CI = (1.32, 3.38), p = 0.002 OR (20-39) = 1.72 95%CI = (1.08, 2.74), p = 0.023 **survival***, vs. ≥ 40/yr HR (<5) = 1.34 95%CI = (1.09, 1.65), p = 0.006 HR (5-19) = 1.24 95%CI = (1.09, 1.42), p =0.002 HR (20-39) = 1.10 95%CI = (0.97, 1.26), p = 0.14	NR	NR	NR	NR	NR	NR
Toomey et al. 2016 [33]	**30D** LVH = 3/50 (6%) HVH = 2/50 (4%) p = NS	(median, mean ± SD) **NOS** LVH = 7, 11 ± 13.1 HVH = 8, 12 ± 13.2 p = 0.01 **ICU** LVH = 3, 7 ± 10.1 HVH = 1, 4 ± 11.1 p = 0.01	NR	NR	NR	**30D-readmission** LVS = (19%) HVS = (20%) p = NS	NR
Shah et al. 2016 [21]	**IH** LVH = 2/20 (10%) MVH = 1/44 (2.2%) HVH = 0/136 (0%) p = 0.007	**NOS** LVH = 11.8 ± 3.4 MVH = 11.3 ± 2.9 HVH = 7.9 ± 1.7 p < 0.001	**CD>III** LVH = 3/20 (15%) MVH = 2/44 (4.5%) HVH = 3/136 (2.2%) p = 0.024	**ISGPF** LVH = 3/20 (15%), MVH = 7/44 (15.9%), HVH = 5/136 (2.6%), p = 0.01 Grades also available	NR	NR	NR
O'Mahoney et al. 2016 [22]	**IH*** (by states) New York, vs. LVH OR (Medium) = 0.47, 95%CI = (0.30, 0.73) OR (High) = 0.39, 95%CI = (0.22, 0.70) OR (Very high) = 0.23, 95%CI = (0.09, 0.55) California, vs. LVH OR (Medium) = 0.63, 95%CI = (0.43, 0.92) OR (High) = 0.41, 95%CI = (0.25, 0.67) OR (Very high) = 0.46, 95%CI = (0.15, 1.40) Florida, vs. LVH OR (Medium) = 0.66, 95%CI = (0.39, 1.11) OR (High) = 0.35, 95%CI = (0.18, 0.68) OR (Very high) = 0.34, 95%CI = (0.16, 0.73)	**POD±14*** (by states) New York, vs LVH OR (Medium) = 0.59, 95%CI = (0.47, 0.75) OR (High) = 0.50, 95%CI = (0.37, 0.67) OR (Very high) = 0.33, 95%CI = (0.19, 0.56) California, vs. LVH OR (Medium) = 0.64, 95%CI = (0.52, 0.78) OR (High) = 0.64, 95%CI = (0.49, 0.85) OR (Very high) = 0.68, 95%CI = (0.43, 1.07) Florida, vs LVH OR (Medium) = 0.61, 95%CI = (0.45, 0.84) OR (High) = 0.52, 95%CI = (0.35, 0.77) OR (Very high) = 0.48, 95%CI = (0.31, 0.75)	NR	NR	NR	NR	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Sutton et al. 2015 [28]	**IH** VLVH = 68 (3.5 %) LVH = 44 (2.2 %) MVH = 27 (1.4 %) HVH = 29 (1.5 %) VHVH= 26 (1.3 %) p < 0.001	(median, IQR) **NOS** VLVH = 11 (8–17), LVH = 9 (7–14), MVH = 9 (7–14), HVH = 9 (7–13), VHVH = 8 (6–13) p < 0.001 **ICU** VLVH = 2 (0–4), LVH = 1 (0–2), MVH = 1 (0–2), HVHV = 1 (0–2), VHVH = 1 (0–2) p < 0.001	NR	NR	NR	**30D-readmission*** vs. VLVH HR (LVH) = 0.97, p = NS 95%CI = (0.83, 1.15) HR (MVH) = 0.93, p = NS 95%CI = (0.79, 1.10) HR (HVH) = 0.84, p = 0.04 95%CI = (0.71, 0.96) HR (VHVH) = 0.78, p = 0.004 95%CI = (0.66, 0.93)	NR
Ryan et al. 2015 [49]	**IH** surgeon volume category change beta = -1.49, R2 = 0.53, p < 0.001	**POD** surgeons volume category change beta = -1.0571, R2 = 0.85, p = 0.029	NR	NR	NR	NR	NR
Yoshioka et al. 2014 [58]	**IH*** vs. VLVH OR (LVH) = 0.78 95%CI = (0.56, 1.08), p = 0.131 OR (MVH) = 0.61 95%CI = (0.43, 0.86), p = 0.006 OR (HVH) = 0.53 95%CI = (0.37, 0.76), p = 0.001 OR (VHVH) = 0.25 95%CI = (0.14, 0.43), p < 0.001	**POD*** vs. VLVH baseline= 43.9 ± 24.3, beta (LVH) = −3.4 95%CI = (−5.4, −1.3), p = 0.001 baseline: = 40.5 ± 22.9 beta (MVH) = −6·6 95%CI = (−8.6, −4.4), p < 0.001 baseline = 37.2 ± 21.7 beta (HVH) = −7.0 95%CI = (−9.5, −4.5), p < 0.001 baseline = 36.9 ± 21.9 beta (VHVH) = −11.3 95%CI = (−14.6, −8·0), p < 0.001 baseline = 32.8 ± 19.2	NR	NR	NR	NR	NR
Shi et al. 2014 [20]	NR	**Hospital POD*** LVH = 40±25.5, MVH = 40±20.6, HVH = 36±22.8 vs. LVH, MVH = -2.2, p < 0.001 HVH = -3.8, p < 0.001 **Surgeon POD*** LVS = 40±23.4, MVS = 37±21.5, HVS = 36±21.2 vs. LVS MVH = -2.7, p < 0.001 HVH = -4.2, p < 0.001	NR	NR	NR	NR	NR
Gooiker et al. 2014 [41]	**30D, 60D**, NS **Survival***, vs. 0-10, Ref HR (Vol.11-19) = 0.91, 95%CI = (0.74, 1.10), p = 0.326 HR (Vol.20+) = 0.70, 95%CI = (0.58, 0.84), p < 0.001	NR	NR	NR	NR	NR	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Enomoto et al. 2014 [59]	**Hospital & surgeon IH*** vs. LVS/LVH OR (LVS/HVH) = 0.54, 95%CI = (0.33, 0.90), p = 0.018 OR (HVS/LVH) = 0.56, 95%CI = (0.27, 1.19), p = 0.130 OR (HVS/HVH) = 0.32, 95%CI = (0.20, 0.49), p < 0.001	**TAD*** Hospital & surgeon volume vs. LVS/LVH OR (LVS/HVH) = –2.44, 95%CI (–3.59 - –1.30), p<0.001 OR (HVS/LVH) = –2.97, 95%CI = (–4.42 - –1.51), p<0.001 OR (HVS/HVH) = –5.65, 95%CI = (–6.70 - –4.60), p<0.001	NR	NR	NR	NR	NR
Ansari et al. 2014 [34]	**30D*** LVH = 1/25 (4%) MVH = 2/876 (2%) HVH= 0/110 (0%) p=0.066	**POD** median (range) LVH = 16 (9-89) MVH = 15 (8-62) HVH = 13 (6-78) p=0.010	**CD>III*** LVH = 5/25 (20%) MVH = 14/86 (16.3%) HVH = 19/110 (17.3%) p = 0.872	**ISGPF-POPF*** Grade B HVH = 0/25 (0.0%) MVH = 5/86 (5.8%) HVH = 8/110 (7.3%) Grade C LVH = 4/25 (16.7%) MVH = 8/86 (9.3%) HVH = 3/110 (2.7%) p = 0.238	**DGE (ISGPG)***, p = 0.588 **PPH (ISGPG)***, p = 0.022	**Reoperation*** LVH = 2/25 (8.3%) MVH = 3/86 (3.5%) VHV = 1/110 (0.9%) p = 0.041	NR
Addeo et al. 2014 [43]	**60D** LVH = 19/51, MVH = 22/51, HVH = 10/51 p = 0.9778	NR	**CD>IIIb*** vs. 20+ OR (20-) = 1.39, 95%CI = (1.09, 1.78), p = 0.0077	**ISGPF-POPF(CR)*** vs. 10+ RR (10-) = 1.92, 95%CI = (1.07, 3.45), p = 0.0286	**DGE (ISGPG)*** vs. 10+ RR (10-) = 1.70, 95%CI = (1.13, 2.55), p = 0.107	NR	NR
Schneider et al. 2013 [53]	**IH*** vs. LVS, RR (MVS) = 0.56, 95%CI = (0.41, 0.78) RR (HVS) = 0.46, 95%CI = (0.29, 0.79)	**POD±14*** vs. LVS OR(MVS) = 0.69, 95%CI = (0.82-0.95), p < 0.001 OR(HVS) = 0.68, 95%CI = (0.61-0.75), p < 0.001 vs. LVH OR(MVH) = 0.88, 95%CI = (0.82-0.95), p = 0.002 OR(HVH) = 0.73, 95%CI = (0.66-0.81), p < 0.001	NR	NR	NR	NR	NR
Hyder et al. 2013 [47]	**IH** by hospital volume VLVH = 13.0%, LVH = 7.6%, MVH = 5.7%, HVH = 4.6%, p<0.001 **IH** by surgeon volume VLVH = 12.6%, LVH = 8.2%, MVH = 5.8%, HVH = 4.0%, p<0.001 **90D** by hospital volume VLVH = 17.2%, LVH = 14.1%, MVH = 8.7%, HVH = 8.0%, p<0.001 **90D** mortality by surgeon volume VLVH = 16.7%, LVH = 12.1%, MVH = 11.1%, HVH = 7.7%, p<0.001	**TAD** VLVH = 17, LVH = 16, MVH = 14, HVH = 13, p<0.001 VLVS = 18, LVS = 16, MVS = 14, HVS = 12.5, p<0.001 **Readmission days** VLVH = 7.0, LVH = 5, MVH = 7.0, HVH = 4, p<0.001 VLVS = 6.4, LVS = 3.6, MVS = 2.5, HVS = 2.5, p<0.001	NR	NR	NR	**30D-readmission** vs. VLVH OR (LVH) = 1.33, 95%CI = (0.82, 2.14) OR (MVH) = 1.30, 95%CI = (0.83, 2.03) OR (HVH) = 1.85, 95%CI = (1.22, 2.80) Surgeon volume: NS	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Pecorelli et al. 2012 [35]	**30D** LVS = 11/252 (4.3%) HVS = 14/358 (3.9%) p = 0.84	**POD** (mean ± SD) LVS = 16.9 ± 9.6, HVS = 15.5 ± 9.7 p = 0.11	NR	**ISGPF-POPF*** vs. HVS OR(LVS) = 1.79, 95% CI = (1.11, 2.91), p = 0.017	**(other definition)** HVS = 11.5%, LVS = 11.9%, p = NS	NR	NR
Kim et al. 2012 [60]	**IH*** vs. VLVH OR (LVH) = 0.59, 95%CI = (0.36, 0.98), p = 0.042 OR (MVH) = 0.61, 95%CI = (0.37, 1.01), p = 0.056 OR (HVH) = 0.13, 95%CI = (0.05, 0.32), p < 0.001 OR (VHVH) = 0.16, 95%CI (0.06, 0.41), p < 0.001	NR	NR	NR	NR	NR	NR
de Wilde et al. 2012 [61]	**IH*** vs. 20+ OR (5-) = 5.08, 95% CI (2.84, 9.07) OR (5-10) = 3.22, 95% CI (2.00, 5.18) OR (11-19) = 2, 95% CI (1.23, 3.25)	NR	NR	NR	NR	NR	NR
Schmidt et al. 2010 [36]	**30D** LVS = 4% HVS = 2% p = 0.09	NR	NR	**ISGPF-POPF** LVS = 11% HVS = 12% p = 0.60	NR	NR	NR
Kennedy et al. 2010 [44]	**60D*** adjusted ES not reported, p = 0.04	**POD** adjusted ES not reported, p = 0.02	**CD>III*** Adjusted ES not reported, p = 0.009	NR	NR	NR	NR
Schell et al. 2008 [29]	**IH** HVH = LVH = 4% **Survival, 3Y** LVH = 31.2%, HVH = 18.3%, p = 0.035 **Survival, 5Y** LVH = 18.3% HVH = 19%, p = 0.096	**POD** (mean ± SD) LVH = 24.5 ± 24, HVH = 16.1 ± 23.5 p <0.0001 **ICU** (mean ± SD) LVH = 8.8 ± 21.6, HVH = 2.1 ± 7 p < 0.001	NR	**ISGPF-NOS** LVH = 4/68 (5.9%) HVH = 38/301 (12.6%) p = 0.14	**DGE(NOS)**, p = 0.754 **PPH(NOS)**, p = 0.140	NR	NR
Rosemurgy et al. 2008 [51]	**IH** (surgeon volumes in 33 months) Q1(1-3), (95-97) = 5.5%, (03-05) = 12.3% Q2(4-9) (95-97) = 9.9%, (03-05) = 7.3% Q3(10 - 16) (95-97) =0.0%, (03-05) = 7.1% Q4(≥ 17) (95-97) = 2.6%, (03-05) = 2.2%	**IHD** (surgeon volumes in 33 months) Q1(1 - 3) (95-97) = 23, (03-05) = 18 Q2(4 - 9) (95-97) = 20, (03-05) =16 Q3(10 - 16) (95-97) = 18, (03-05) =15 Q4(≥ 17) (95-97) = 17, (03-05) 15	NR	NR	NR	NR	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Pal et al. 2008 [37]	**30D** vs. HVH RR = 1.60, 95%CI = (1.10, 2.41), p = 0.016	NR	NR	NR	NR	NR	NR
Topal et al. 2007 [50]	**IH** vs. (1-2) OR (3-5) = 0.88, 95%CI = (0.54, 1.5) OR (6-10) = 0.93, 95%CI = (0.49, 1.8) OR (11-20) = 0.49, 95%CI = (0.26, 0.91) OR (> 20) = 0.41, 95%CI = (0.22, 0.77) model p = 0.011	**POD** ES not reported, p = 0.027	NR	NR	NR	NR	NR
Ho et al. 2006 [24]	**IH*** vs. LVH OR (HVH) = 0.85, 95%CI = (0.74, 0.097), p = 0.017 vs. LVS OR (HVS) = 0.80, 95%CI = (0.69, 0.92), p = NR	NR	NR	NR	NR	NR	NR
Urbach et al. 2003 [121]	**30D*** vs. Q4 RR (Q1) = 2.2, 95%CI = (1.0, 4.7) RR (Q2) = 1.9, 95%CI = (0.8, 4.4), RR (Q3) = 2.0, 95%CI = (0.9, 4.6),	NR	NR	NR	NR	NR	NR
Ho et al. 2003 [25]	**IH*** vs. HV = 1/yr OR (2-3) =0.84, 95%CI = (0.66, 1.08), p = 0.18 OR (4-9) =0.70, 95%CI = (0.53, 0.93), p = 0.01 OR (10+) = 0.34, 95%CI = (0.20, 0.56), p < 0.001 Experience in years, unit increase OR = 0.94, 95%CI = (0.91, 0.98), p = 0.001	NR	NR	NR	NR	NR	NR

Author Year	Mortality outcomes	Length of stay	Overall Morbidity	Complication - Fistula	Complication – Others	Reoperation and readmission	Others
Nordback et al. 2002 [62]	**IH*** Surgeons volume, unit increase? OR = 1.30, 95%CI = (0.94, 1.80) Hospital volumes, unit increase? OR = 0.97, 95%CI = (0.85, 1.10)	**NOS** (median, range) hospital volume LVH = 23 (8, 100), MVH = 23 (7, 81), HVH = 18 (8, 58), p < 0.05 surgeon volume LVH = 24 (9, 70), MHV = 23 (7, 100), HVH = 18 (8, 63), p < 0.05	**Uncomplicated recovery** Hospital volume LVH = 119/201 (59%), MVH = 55/93 (59%), HVH = 40/56 (71%), p > 0.05 Surgeon volume LVS = 72/125 (58%), MVS = 96/164 (59%), HVS = 46/61 (71%), p < 0.05	NR	NR	**Reoperation*** Surgeon volume, unit increase (unclear) OR = 1.10, 95%CI = (0.88, 1.35) Hospital volume, unit increase (unclear) OR = 1.03, 95%CI = (0.93, 1.14)	NR
Rosemurgy et al. 2000 [52]	**IH** not-adjusted, raw rates reported p = 0.036	**NOS** not-adjusted, raw rates reported p = 0.025	NR	NR	NR	NR	NR
Birkmeyer et al. 1999 [42]	**IH*** VLVH = 16.1%, LVH = 12.7%, MVH = 10.1%, HVH = 4.1%, p < 0.001; **30D*** VLVH = 12.9%, LVH = 9.0%, MVH = 7.3%, HVH = 3.0%, p < 0.001	**NOS*** VLVH = 22, LVH= 21, MVH= 20, HVH= 16, p < 0.001	NR	NR	NR	NR	NR
Birkmeyer et al. 1999 [48]	**Survival*** vs. VLVH HR (LVH) = 0.88, 95%CI = (0.80, 0.97) HR (MVH) = 0.81, 95% CI = (0.74, 0.89) HR (HVH)= 0.69, 95%CI = (0.62, 0.76)	NR	NR	NR	NR	NR	NR
Imperato et al. 1996 [56]	**IH*** vs. Regional (HVH) RR (others) = 5.40, 95%CI = (1.6, 18.2), p = 0.006	(live discharges) **NOS*** Regional (HVH)= 22.3, others (LVH) = 31.8 RD = 7.95, p < 0.001	NR	NR	NR	NR	NR
Gordon et al. 1995 [55]	**IH*** Regional (HVH) = 2.2% Others (LVH) = 13.5% RD = 11.4%, p < 0.001 RR (vs. HVH, unadjusted) = 6.1, 95%CI = (2.9, 12.7), p = NR	(live patients only) **POD*** Regional (HVH) = 22.5, others (LVH) = 27.9 RD = 5.7, p < 0.001 RD (adjusted) = 5.7, p < 0.001 **ICU*** Regional (HVH) = 1.8, others (LVH) =3.8 RD = 2.0, p < 0.001 RD (adjusted) = 1.9, p < 0.001	NR	NR	NR	NR	NR

Abbreviations: **95%CI** = 95% confidence interval, **CD** = Clavien-Dindo classification, **D** = day, **DGE** = delayed gastric emptying, **ES** = effect size, **HR** = hazard ratio, **HVH** = high-volume hospital, **HVS** = high-volume surgeon, **ICU** = intensive care unit, **IH** = in-hospital, **IHD** = in hospital days, **IPD** = inpatient days, **IQR** = interquartile range, **ISGPF** = international study group, **LT/HVH** = long travel/high-volume hospital, **LVH** = low-volume hospital, **LVS** = low-volume surgeon, **M** =median, **MVH** = medium volume hospital, **NOS** = not otherwise specified, **NR** = not reported, **NS** = not significant, **OR** = odds ratio, **POD** = postoperative days, **POPF** = postoperative pancreatic fistula, **PPH** = post-pancreaticoduodenectomy haemorrhage, **Q** = quartile, **R^2** = coefficient of determination, **RD** = risk difference, **Ref** = reference, **RR** = relative risk, **SD** = standard deviation, **SSI** = surgical site infection, **ST/LVH** = short travel/low-volume hospital, **TAD** = total admission days, **VHVH** = very high-volume hospital, **VLVH** = very low-volume hospital, **Vol** = volume, **vs** = versus, **Yr** = year.

Notes: Tumour stage has been classified according to TNM system; *adjusted for confounding effect.

Appendix 4 Review Working Group and Authors

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Appendix 5 Studies excluded at full-text review

Wrong population

(e.g. not patients receiving the Whipple surgery, sub-group or mixed populations)

1. Kostalas M, Nageswaran H, Froghi S, Riga A, Kumar R, Menezes N, et al. Centralisation for resection of the pancreatic head: A comparison of operative factors and early outcomes during the evolving unit and tertiary unit phases at a UK institution. Am J Surg. 2018;216(2):310-3.
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Wrong intervention

(e.g. not the Whipple Procedure, or no Whipple procedure specific investigations)

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Wrong comparator

(note that this category is not applicable in this review)

(no studies)

Wrong outcomes

(e.g. outcomes not relevant, cannot be extracted)

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Wrong study type

(e.g. non-observational studies)

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Full-text unavailable

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