Pancreatoduodenectomy for pancreatic head tumors in the elderly–systematic review and meta-analysis

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ABSTRACT

Objective: This meta-analysis aims to assess the safety of pancreatoduodenectomy in elderly population, primarily focusing on morbidity and mortality.

Summary Background Data: The age at which patients are undergoing pancreatoduodenectomy is increasing worldwide. The data on the outcome of this surgical procedure in the elderly is constantly expanding.

Methods: We searched the Medline, Embase and Cochrane databases to identify eligible studies. The most recent search was performed on 10th April 2017. Inclusion criteria were: (1) comparison of the characteristics and perioperative outcomes of older patients versus younger patients undergoing pancreatoduodenectomy; (2) objective evaluation of mortality or overall morbidity; and (3), publication in English. Exclusion criteria were: (1) a lack of comparative data; (2) a lack of primary outcomes or insufficient data to analyze; (3) a focus on procedures other than pancreatoduodenectomy; or (4), the impossibility of extraction of data specifically concerning pancreatoduodenectomy. Primary outcomes were overall morbidity and mortality. Secondary outcomes analyzed postoperative complications, R0 rate and length of hospital stay.

Results: 45 eligible studies were chosen, with a combined total of 21,295 patients. Older patients compared to younger patients had a higher risk of death (2.26% vs. 4.54%; RR: 2.23; 95% CI 1.74–2.87) and a higher complication rate (47.23% vs. 39.35%; RR: 1.17; 95% CI 1.12–1.24). There were no differences in pancreatic fistula occurrence (p = 0.27), bile leakage (p = 0.81), postoperative hemorrhage (p = 0.08), or R0 rate (p = 0.92).

Conclusions: Our review confirms, that in the case of pancreatoduodenectomy, advanced age is a risk factor for increased non-surgical morbidity and, by extension, higher mortality.

INTRODUCTION

In recent decades we have witnessed significant improvements in medical care and continuous development of medical technology. As a result, a higher life expectancy can be observed in most populations [1]. The elderly constitute a high-risk group of candidates for surgery, most commonly with accompanying comorbidities and reduced health capacity [2]. In addition, age is one of the main risk factors for cancer development, including pancreatic

neoplasms [3]. A 2016 report by Ferlay *et al*. suggested that in EU countries more people annually from pancreatic cancer than breast cancer [4]. After lung and colorectal cancers, pancreatic cancer may soon become the third most common cause of cancer-related death in the European Union. According to statistics, more than ¾ of patients with pancreatic cancer and other periampullary neoplasms are older than 60 years of age and more than a half are above 70 years of age. This means that the number of elderly patients seeking help from surgery will inevitably continue to rise [5, 10–53].

Improvements in the operative technique of pancreatoduodenectomy (PD), along with improvements in perioperative care, have led to reduced mortality [6]. The rate, however, of postoperative complications of 40% or above is still relatively high [7]. Increased overall mortality among elderly population remains the greatest concern. In fact, due to the aggressive nature of the tumor (median survival in unresected pancreatic cancer is less than 12 months), a lack of alternative treatment options, and an ageing population, there is less reluctance to perform PD in elderly candidates than might otherwise be expected [8, 9]. Therefore, it is important to evaluate the risk of mortality, morbidity and adverse events in elderly patients undergoing PD. We aimed to review systematically the available published literature and conduct a meta-analysis comparing the outcomes of PD in the elderly with the young.

RESULTS

An initial reference search yielded 2,043 articles. After removing 503 duplicates, 1,540 articles were evaluated through titles and abstracts. This produced 143 articles suitable for full-text review. Finally, 45 articles were studies eligible for data extraction, with a combined total of 21,295 patients (3,824 from the older population and 17,471 from the younger population) [5, 10–53]. A flowchart of the analyzed studies is presented in Figure 1. Since the majority of studies scored at least 6 out of 9 in Newcastle-Ottawa Scale (NOS), the average quality of studies included is high. Baseline information about the analyzed studies is presented in Supplementary Table 1. The funnel plot of publication bias is presented in Supplementary Figure 1. The cone is asymmetrical which may suggest a publication bias for studies regarding <70 vs. >70 groups. This possible bias, however, is only associated with articles that had a small numbers of participants, and therefore, would have had little impact on results in general.

Mortality was reported in 42 studies, with a total of 11,615 patients (2,180 patients from the elderly population and 9,435 patients from the younger population). There was a significantly lower rate of mortality among younger patients: 213/9435 (2.26%) vs. 99/2180 (4.54%) among older patients, RR: 2.23; 95% CI 1.74–2.87, $p < 0.001$ (Figure 2). Subgroup analysis revealed a similar pattern for the age cut-offs 80, 75, and 70, but not 65; however, the 65-year old cut-off was used in only 2 studies, with a low number of patients responsible for 1.2% of the total effect.

Overall morbidity was reported in 38 studies, involving 19,043 patients (3,301 older patients and 15,742 younger patients). A significant difference was found between older and younger patients: 1,559/3,301 (47.23%) vs. 6,194/15,742 (39.35%): RR 1.17; 95% CI 1.12–1.24, $p < 0.001$. There were no differences in studies using age cut-offs of 65 or 75 years (Figure 3).

Pancreatic fistula occurrence was reported in 37 studies. No significant differences between older and younger populations were found: 372/2,001 (18.59%) vs. 1,399/9,141 (15.3%), $p = 0.27$; 95% CI 0.95–1.20 (Figure 4). Heterogeneity was low except for studies that had 65 years old as the age cutoff ($I^2 = 90\%$).

Bile leakage was reported in 26 studies. Older patients did not differ significantly from younger patients: 30/1,157 (2.59%) vs. 232/6,899 (3.36%), $p = 0.81$; 95% CI 0.71–1.54; the same was true for subgroup analysis (Figure 5). There was no heterogeneity across studies.

Delayed gastric emptying (DGE) was reported in 33 studies, looking at a total of 9,748 patients. It occurred more frequently among older patients: 345/1,807 (19.09%) vs. 1,328/7,941 (16.72%); RR = 1.17 95% CI 1.03–1.33, $p = 0.01$. Heterogeneity in general was low, although it was moderate ($I^2 = 52\%$) for the highest age cut-off. Subgroup analysis showed that the difference was significant only for the age cut-off of 70 years old (Figure 6).

Postoperative hemorrhage was reported in 28 studies and no significant differences were observed: 108/1,474 (7.33%) vs. 276/4,623 (5.97%), $p = 0.08$; 95% CI 0.98–1.52 (Figure 7).

Surgical site infections (SSI) were reported in 26 studies and occurred more frequently in older patients 220/1,336 (16.47%) vs. 669/6,652 (10.06%): RR 1.21; 95% CI 1.05–1.41, $p = 0.009$. Subgroup analysis revealed a significant difference only for the age cut-off of 70 years old. This group comprised almost 70% of analyzed patients. There was no heterogeneity within age cut-off subgroups or across them (Figure 8).

Pulmonary complications were reported in 31 studies and cardiovascular complications were reported in 23 studies. There were significant differences in the prevalence of pulmonary complications: 144/1,755 (8.21%) among older patients vs. 281/8,411 (3.34%) younger patients, RR: 1.71; 95% CI 1.39–2.11, $p < 0.001$. Subgroup analysis revealed no differences in studies with an age cut-off of 65 years old. There was no heterogeneity within the subgroups; however, a moderate heterogeneity was present across them. Cardiovascular complications occurred more frequently among older patients (172/2,019 [8.52%] vs. 248/11,402 [2.18%]); RR: 2.62; 95% CI 2.12–3.23, $p < 0.001$. Subgroup analysis revealed significant differences for the age cut-offs of 70 and 80 years old; heterogeneity was low (Figures 9 and 10).

Length of hospital stay (LOS) was reported in 35 studies; however, 6 of these compared more than 2 groups, rendering them ineligible for meta-analysis. We therefore decided to exclude these studies from our evaluation of this parameter. In the end, our analysis of LOS covered 13,986 patients and revealed significant differences among studied groups. LOS of elderly patients was longer than younger patients: MD: 1.21; 95% CI 0.51–1.91, $p < 0.001$. Subgroup analysis revealed significant differences for the age cut-offs of 65 and 80 years old. Heterogeneity within subgroups ranged from low to high, with the overall heterogeneity being high, $I^2 = 77\%$ (Figure 11).

R0 for pancreatic ductal adenocarcinoma was only reported in 13 studies. There were no differences between older and younger patients, 427/588 (72.62%) vs. 1,794/2,476 (72.46%), $p = 0.92$; 95% CI 0.82–1.25. Heterogeneity was moderate, $I^2 = 51\%$ (Figure 12).

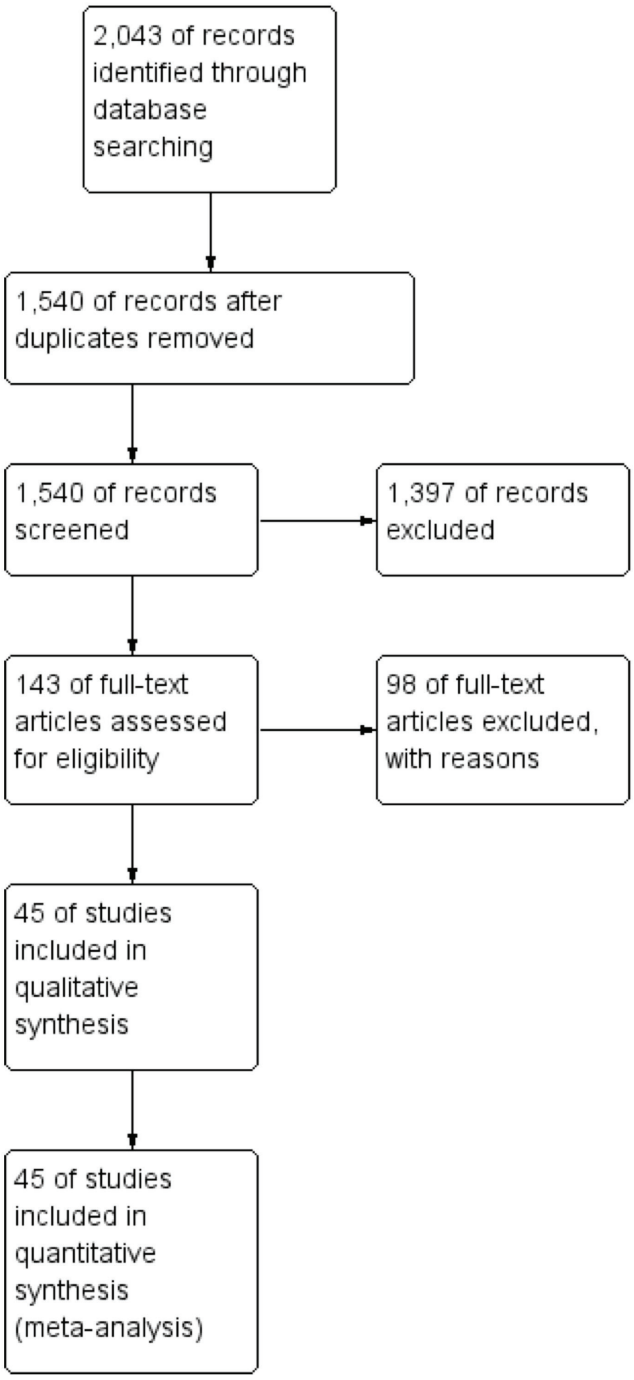

Figure 1: PRISMA flowchart.

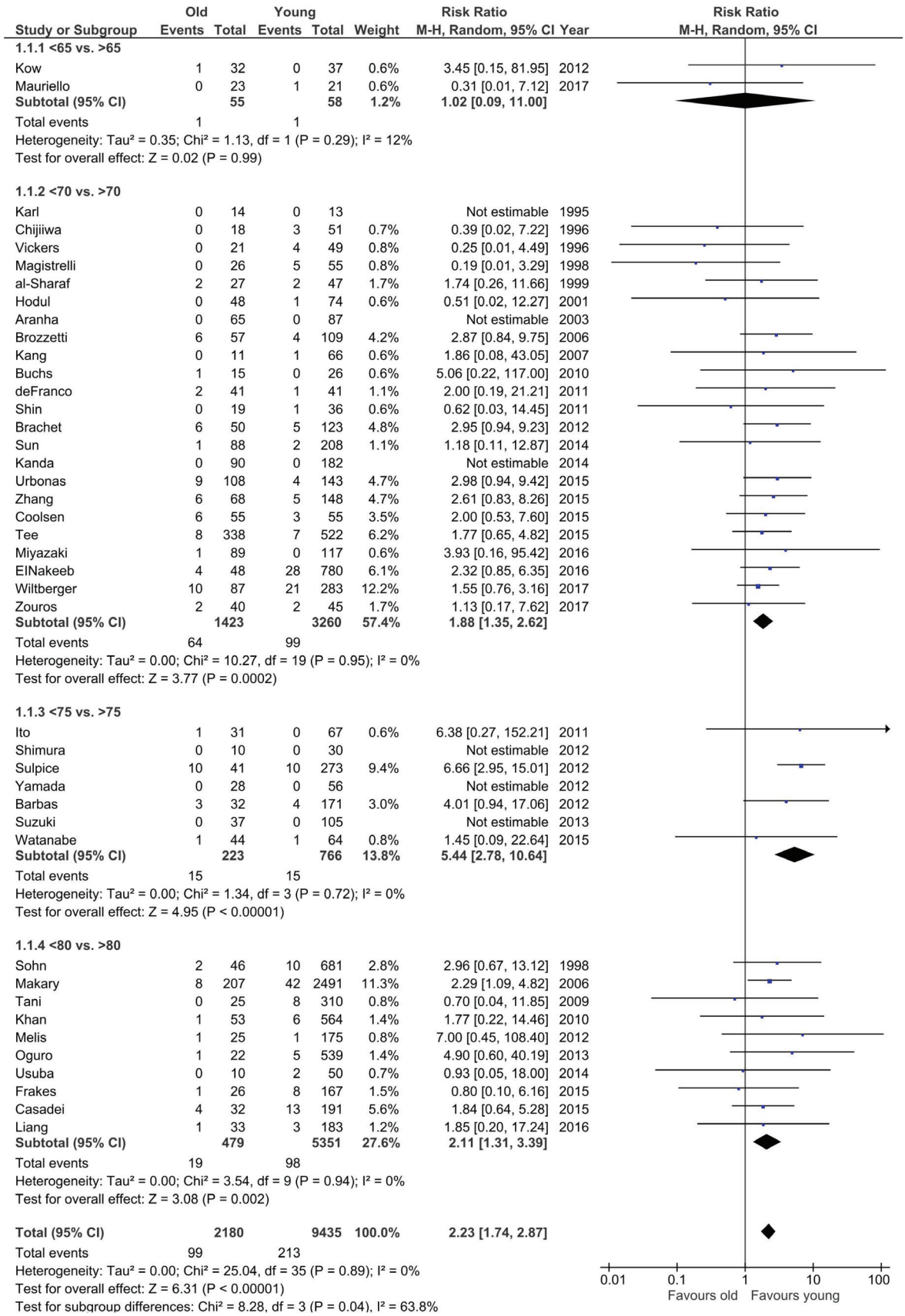

Figure 2: Pooled estimates of mortality comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

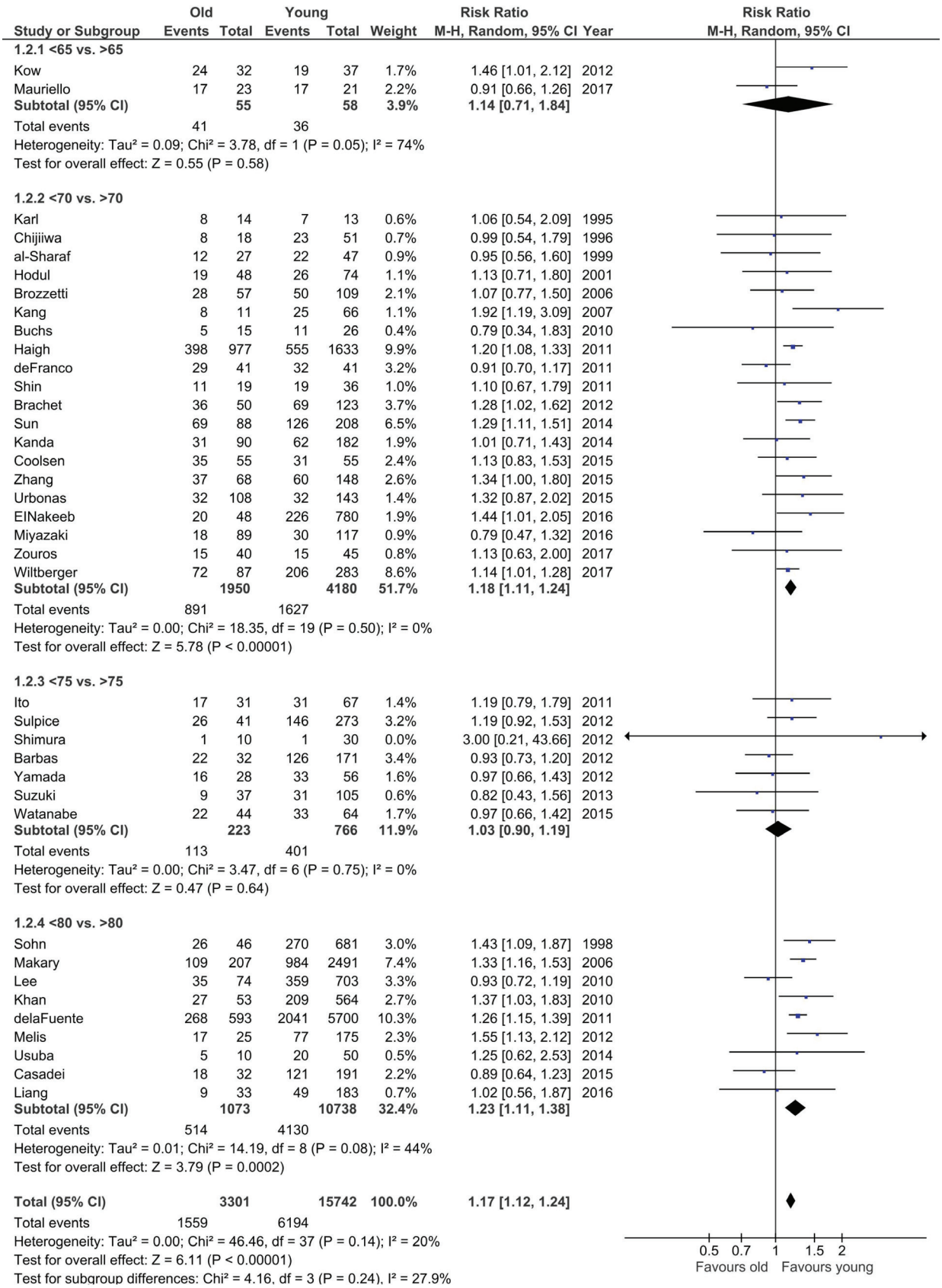

Figure 3: Pooled estimates of overall morbidity comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

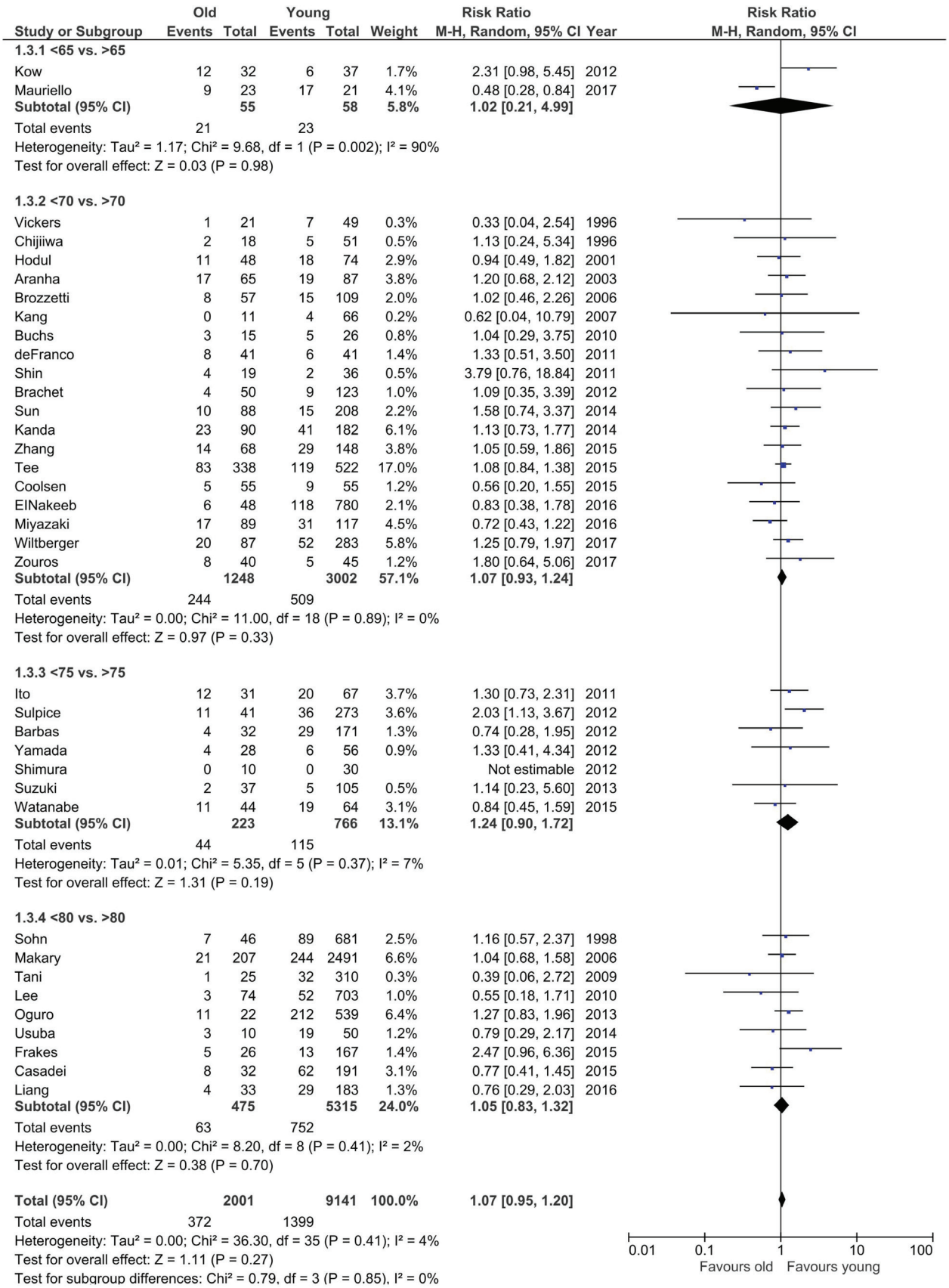

Figure 4: Pooled estimates of pancreatic fistula comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

Readmission was reported in only 8 studies and no age-related differences were observed (Figure 13).

DISCUSSION

Changes in global demographics and an increase in the prevalence of gastrointestinal tumors lead to a rise in the number of extensive surgeries on older patients. This is particularly evident for pancreatic cancer. As long as other treatment strategies remain insufficient, we rely on radical surgery, the only potential cure of pancreatic head malignancies. For this reason, surgery ought to be considered as a valid treatment option for every patient with pancreatic head malignancy, regardless of age.

Our systematic review of 45 studies has shown that among pancreatoduodenectomy patients both postoperative mortality and postoperative morbidity are higher for older patients. An increased rate of non-surgical

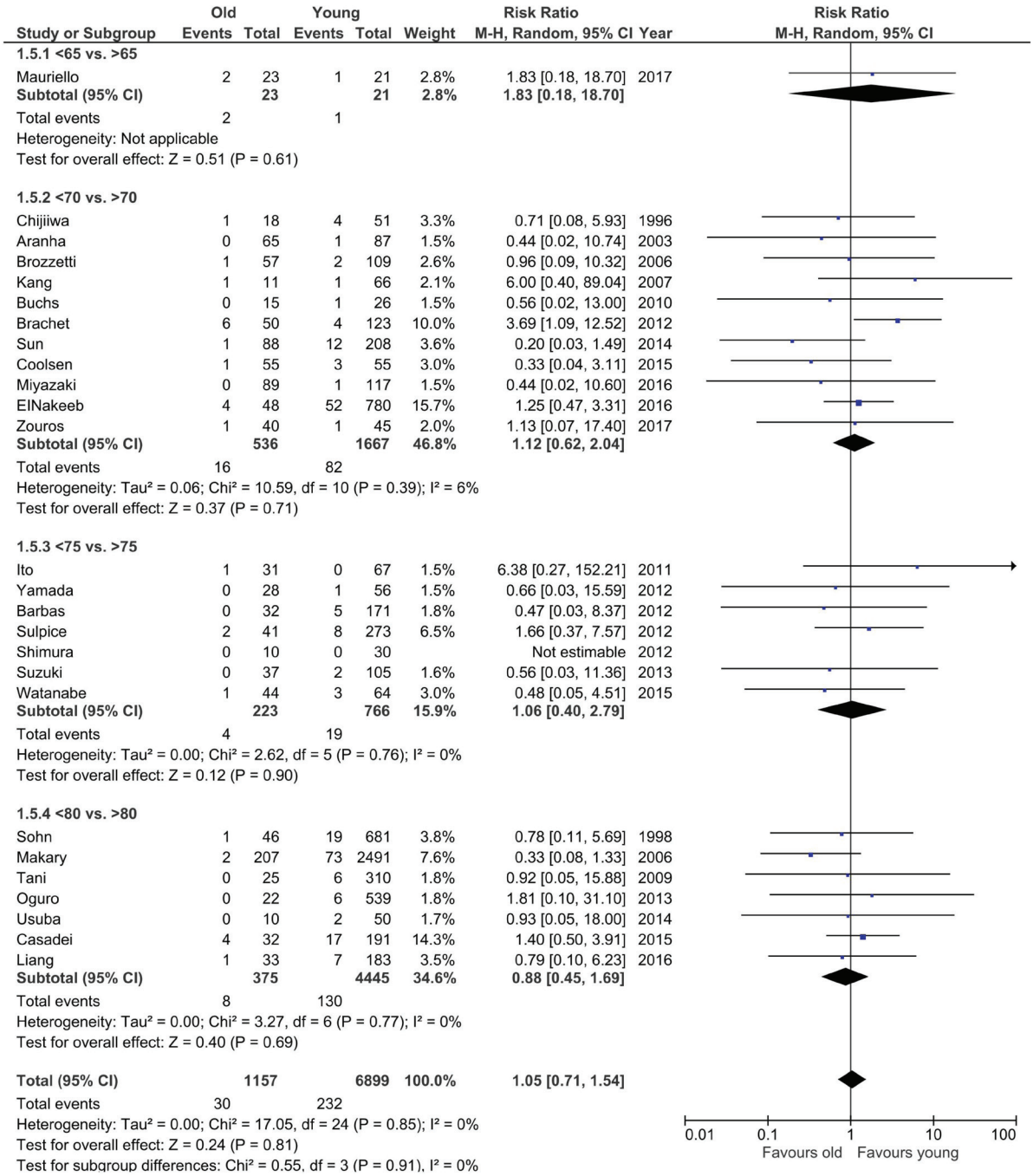

Figure 5: Pooled estimates of bile leakage comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

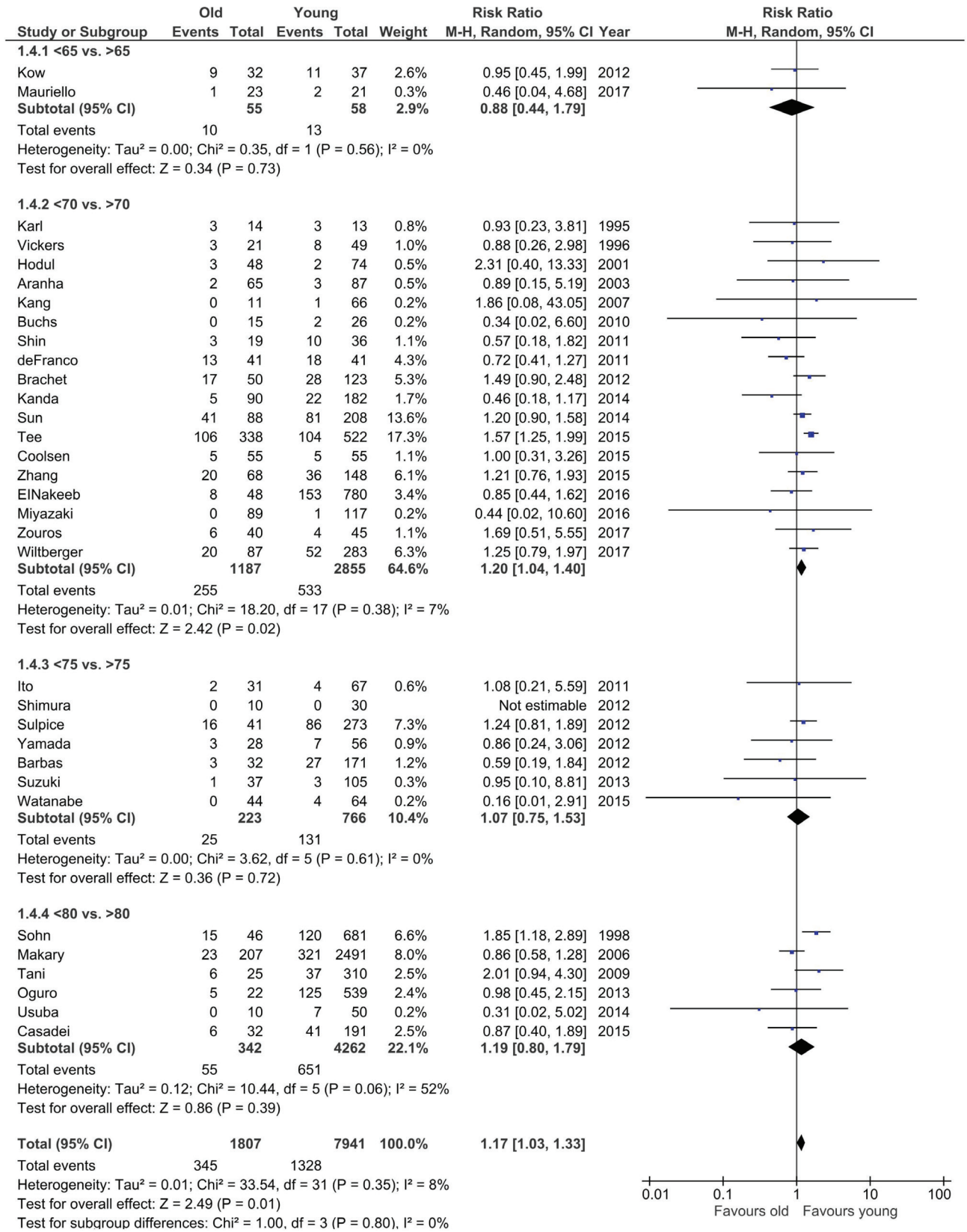

Figure 6: Pooled estimates of delayed gastric emptying comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

complications and a prolonged LOS were observed among older patients. The patient's age does not seem to influence surgical complications related to the procedure itself, such as the rate of fistula, bile leakage, or postoperative hemorrhage. Higher rates of DGE and SSI, however, were observed in the older population.

Patients were eligible based on pancreatic cancer, other tumors and other indications. When analyzing these indications for pancreatoduodenectomy, a slightly larger portion of the elderly candidates (59%/36%/5%) had cancer in comparison to the younger candidates (52%/39%/9%). However, this difference was not statistically significant.

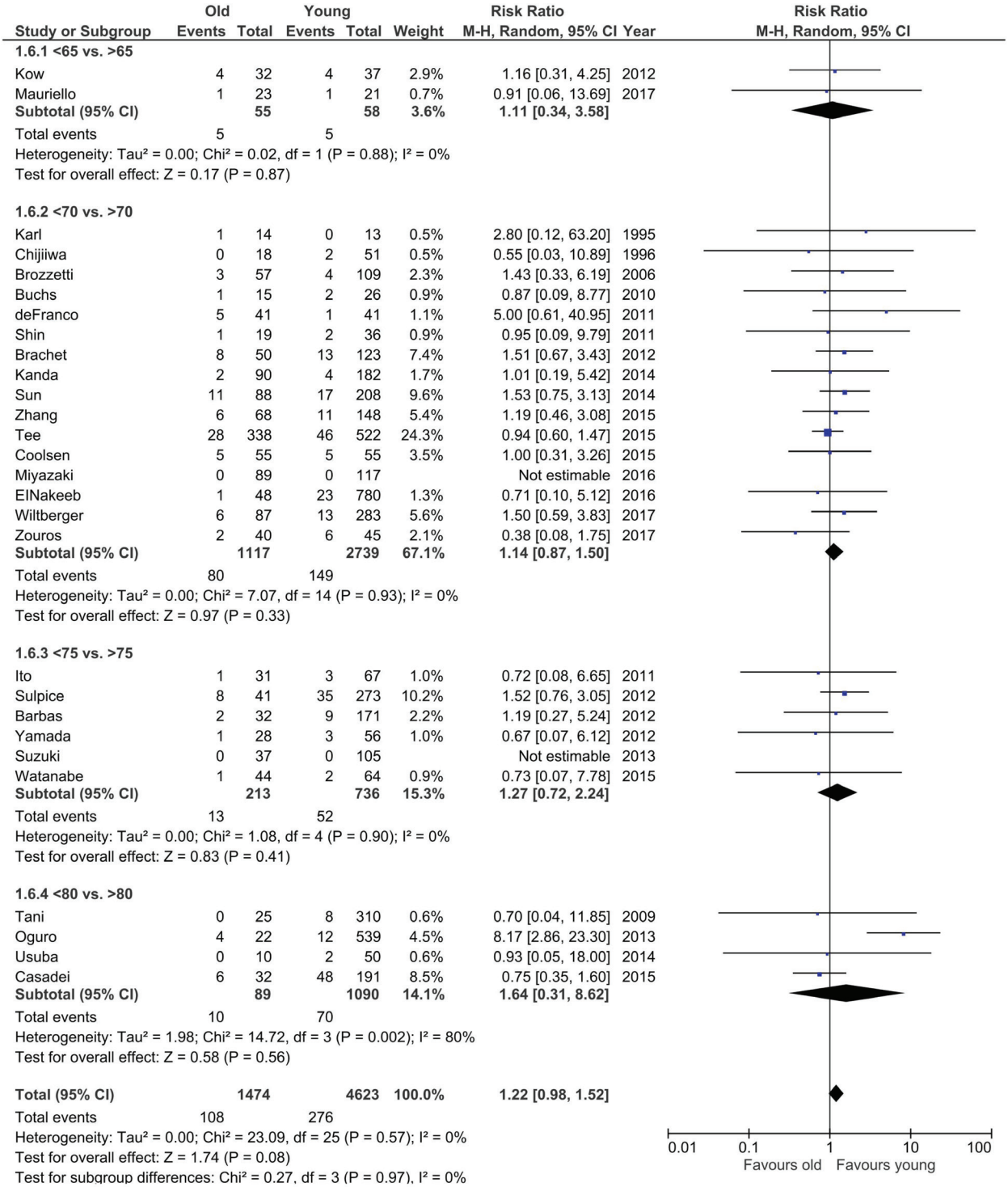

Figure 7: Pooled estimates of postoperative hemorrhage comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

Meta-analysis of all studies reporting mortality confirmed that the risk of perioperative death among older patients is more than twice as high as compared to younger patients (4.54% vs. 2.26%). This was also observed in the subgroup analysis, when different age cut-off points were set. This should be raised during pre-surgery consultations with older patients. Despite the clear difference, mortality among older patients is still considerably low, confirming the current theory that pancreatoduodenectomy is associated with relatively low mortality, even in high-risk patients, despite being one of the most complex and extensive abdominal surgeries, it. On the other hand, the low mortality rate in the included studies is not in line with the data from national databases. According to these databases the mortality rate in the elderly population is usually higher, exceeding even 10% [54, 55]. This

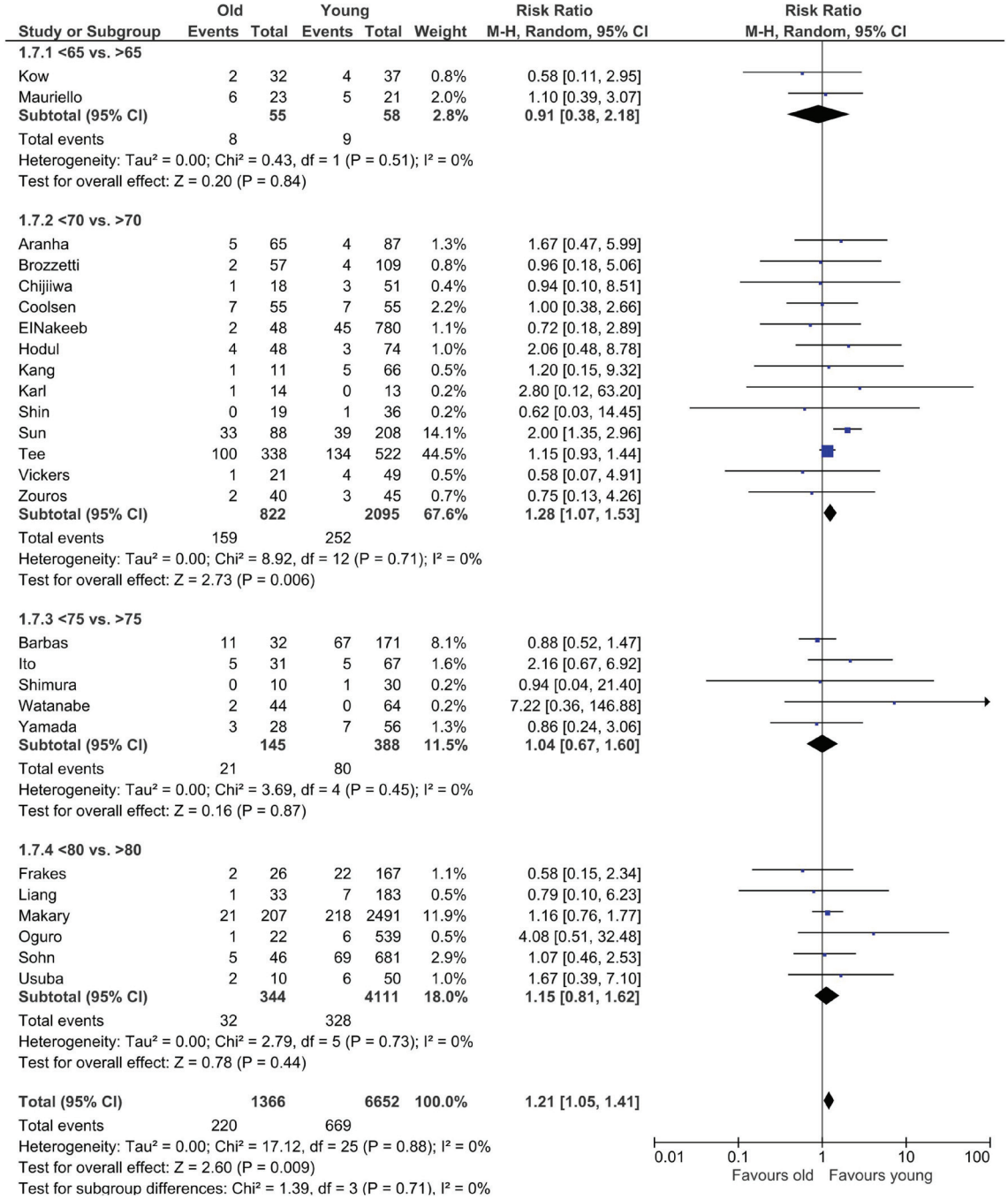

Figure 8: Pooled estimates of surgical site infection comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

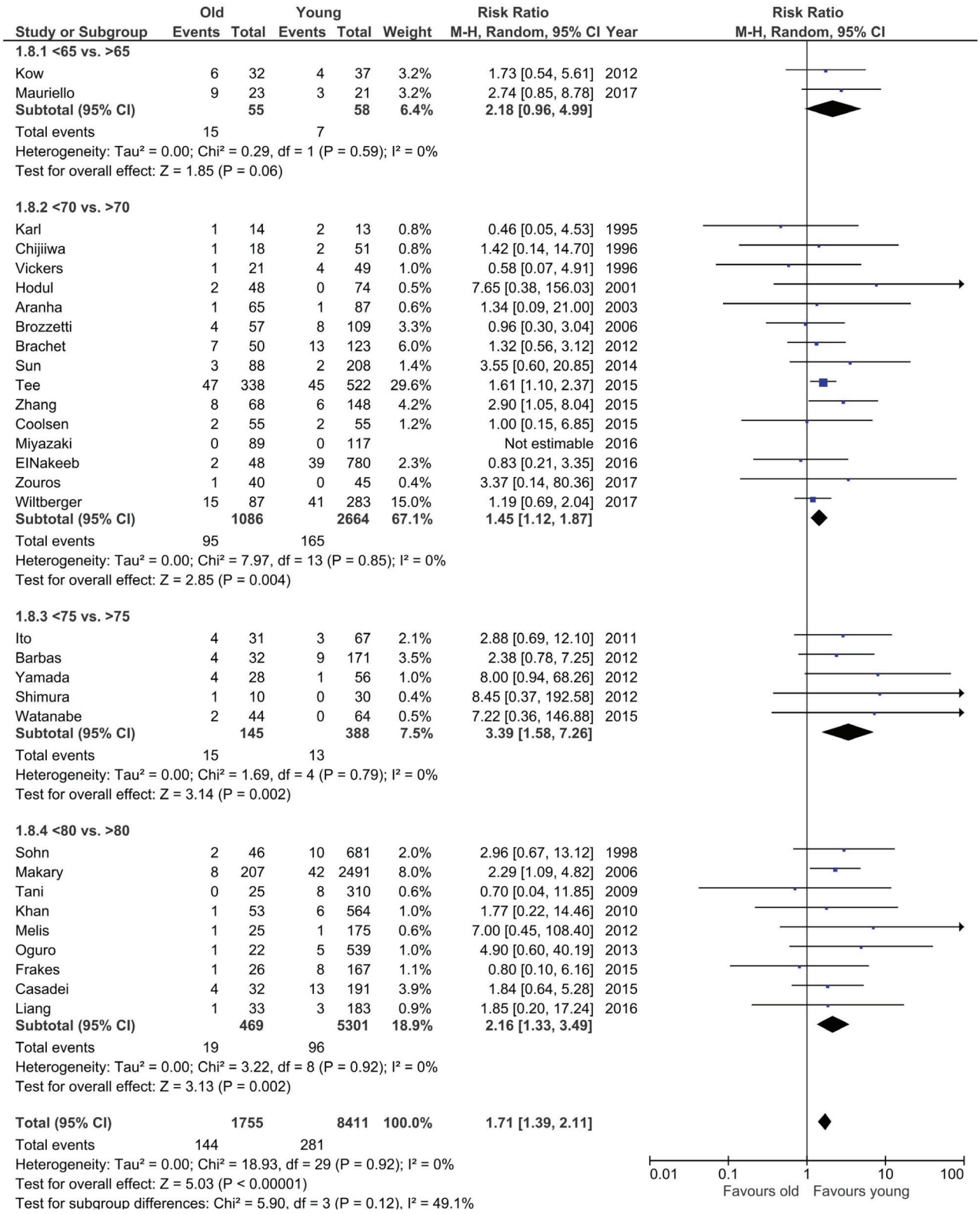

Figure 9: Pooled estimates of pulmonary complications comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

disparity is probably due to the inclusion of low-volume centers reporting increased mortality, whereas most of the included studies in our meta-analysis originated from high-volume centers. It is well established that the annual patient volume of institutions and surgeons is strongly correlated with postoperative mortality [56–58]. Unfortunately, the data on the annual volume was only provided in the minority of included studies and none of them specified the surgeon's annual volume. In addition, a large proportion of the studies were comprised of patients from relatively low volume centers (Supplementary Table 1). On one hand this may bias the results (lower volume = more complications); on the other, it reflects the real clinical situation worldwide, where the majority of PDs are being operated in low volume centres. Even while taking these findings into consideration it seems, that in terms of mortality, the benefits of undergoing surgery for pancreatic head malignancy regardless of age still outweigh the risks. The median survival time in unresected cancer patients can be as low as 12 months, and this is only when palliative chemotherapy is administered [8, 59–61]. Unfortunately, the majority of elderly patients are not, in any way, fit for the most aggressive regimens of chemotherapy. At best, the dose must be reduced due to its toxicity [62–64]. Higher mortality among the elderly should also be taken into consideration in preoperative evaluation of patients with

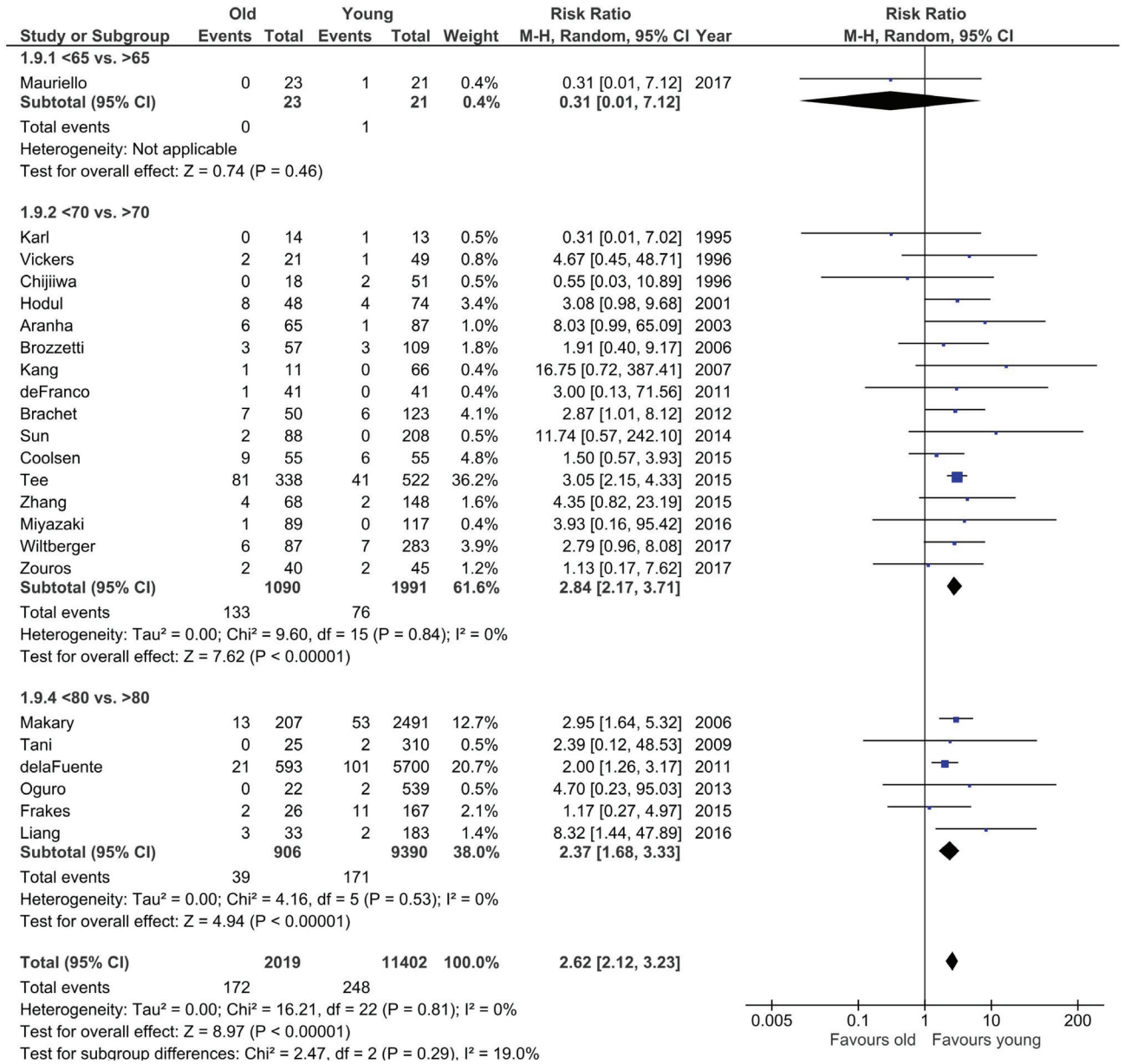

Figure 10: Pooled estimates of cardiovascular comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

tumors that have low or undefined malignant potential. The best treatment strategy for these older patients is yet to be established.

Although postoperative mortality has decreased over the last two decades, morbidity related to pancreatoduodenectomy still remains a serious problem. In our meta-analysis we have shown that the overall complication rate was higher in the elderly (47.23% vs 39.35%). Interestingly, when specific complications were analyzed, it was observed that older age is associated mainly with non-surgical complications as well as DGE and SSI, whereas the rate of all other complications typical for pancreatoduodenectomy (fistula, bile leakage, and postoperative hemorrhage) remained comparable. The relationship between pulmonary disease, cardiovascular disease, and the elderly can help explain differences in postoperative deaths in our analysis [65]. This increase in postoperative deaths is probably associated with a higher prevalence of comorbidities (mainly coronary artery disease, chronic obstructive pulmonary disease, hypertension, liver disease and vascular disease) among the elderly and reduced preoperative care combined with great surgical trauma related to PD [42]. We did not perform an in depth comparison of serious comorbidities

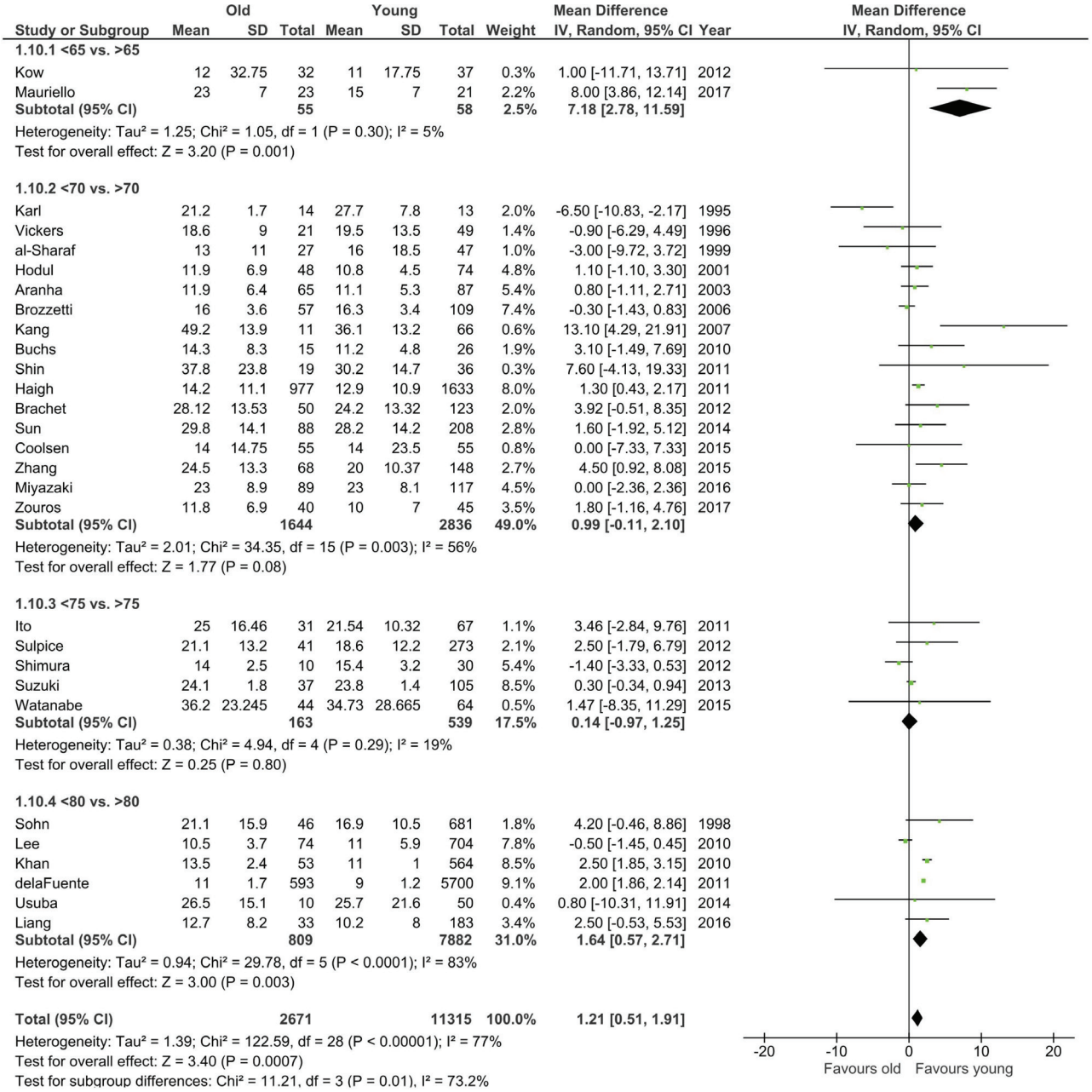

Figure 11: Pooled estimates of length of hospital stay comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom LOS.

between groups; however, they all may result in cardiorespiratory failure, leading to ICU admission in a significant proportion of cases [2, 65]. On the other hand, the insignificant difference in surgical complications may encourage surgeons to perform PD in patients regardless of age. As with every complex and extensive surgical procedure, it is all about common sense and patients' quality of life. Since the outcomes are mainly influenced by non-surgical morbidity, other strategies to improve outcomes should be favored. There is, for instance, strong evidence that the implementation of enhanced recovery after surgery (ERAS) protocols help reduce postoperative surgical trauma [41, 66–68]. ERAS is a multimodal, multidisciplinary approach to the care of the surgical patient that incorporates several pre-, intra-, and postoperative items. When combined together, these are beneficial in terms of LOS, as well as, non-surgical morbidity as seen in other surgical disciplines [69–71]. Although a majority of the changes in ERAS protocol run counter to surgical dogmas and common beliefs, strong scientific evidence supports this modern perioperative approach. In our review, some aspects of perioperative care and resection technique were not investigated. Although there is still a lot of controversy over the use of minimally invasive surgery in pancreatic head resection, it is an alternative strategy that should be investigated specifically in relation to elderly patients [7, 72–75].

A 1.2-days longer LOS was observed in the older group. However, this small difference could be a result of multiple variables and, in fact, seems to be of little clinical relevance, considering the fact that PD is associated with LOS as high as 20 days. What seems to be more important is that once the elderly patient is discharged from surgical ward the risk of readmission is similar to the younger group. In this meta-analysis, readmissions were comparable between groups. However, this finding was based on a limited number of studies and the heterogeneity was moderate.

Our review has some limitations. Apart from the age, we did not precisely analyze demographic differences between groups, such as co-morbidities, ASA score, etc. It is very likely, or even certain, that the elderly group had more co-morbidities. In addition, we did not compare the indications for surgery (pancreatic cancer vs. other periampullary neoplasms). It is well established that the indication for surgery may also have impact on outcomes–for instance patients undergoing PD for advanced pancreatic cancer have a different prognosis

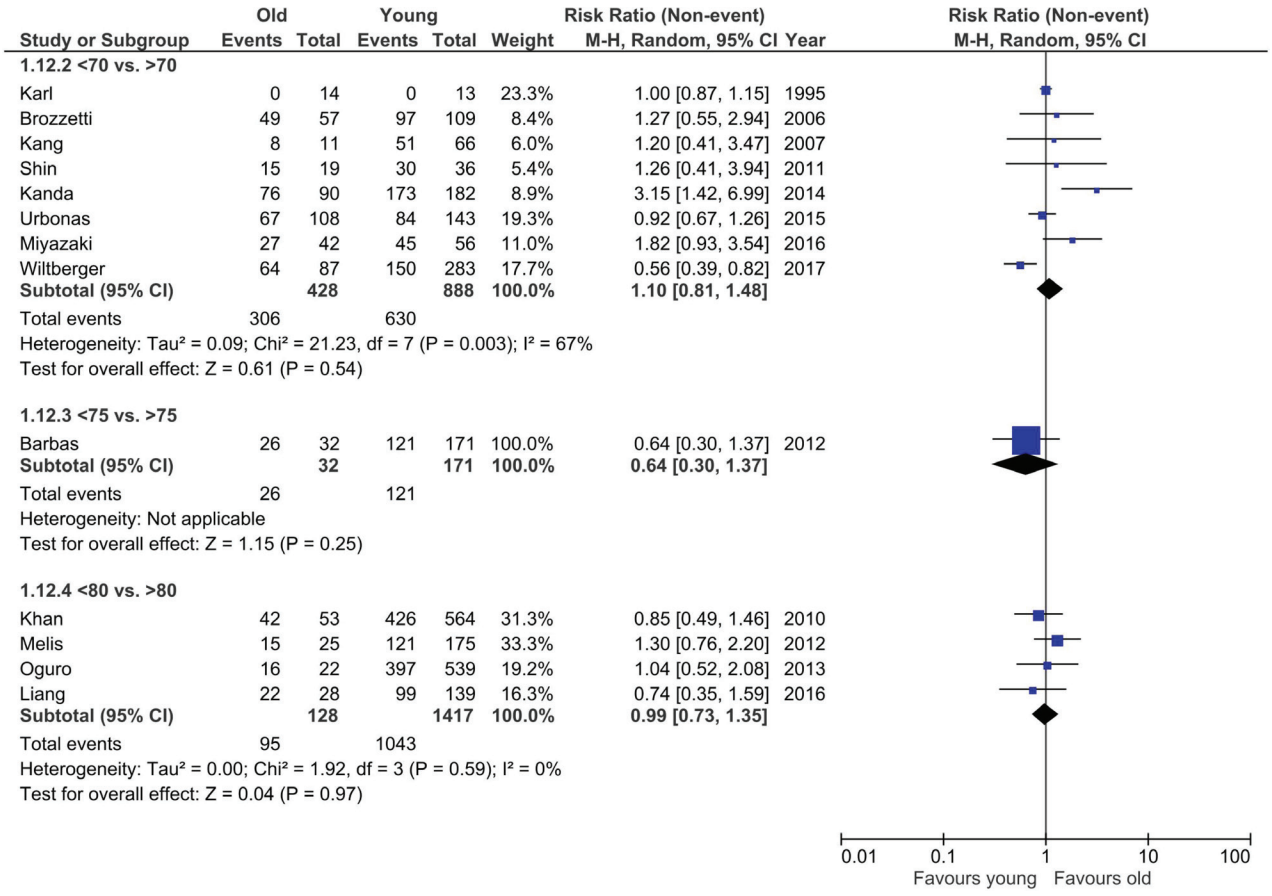

Figure 12: Pooled estimates of R0 resection rate comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

than those with other tumors or benign diseases. The proportion of pancreatic cancer patients in older group was slightly higher (although not statistically significant). Other indications for surgery were duodenal cancer, ampullary carcinoma, distal cholangiocarcinoma, metastasis in the head of pancreas, intraductal papillary mucinous neoplasms, neuroendocrine tumor and chronic pancreatitis We were not able to perform subgroup analysis distinguishing different indications for surgery due to lack of patient level data. So, this limitation also has to be taken into consideration when analyzing results of our meta-analysis. Additionally, the fact that the number of elderly patients receiving adjuvant chemotherapy is lower, one can assume might have influenced survival. Lastly, papers included in the meta-analysis were published over the last two decades during which there have been major changes in pancreatic surgery. That said, in our opinion these aspects did not play a major role in the results.

CONCLUSIONS

Our review confirms that in the case of PD, advanced age is a risk factor for increased non-surgical morbidity and, by extension, higher mortality. These findings are based on a number of moderate or high-quality comparative studies; it is very unlikely that future comparisons will undermine them. Unless other treatment strategies are implemented, the elderly will continue to constitute a group of patients for whom worse outcomes can be expected. However, as long as PD remains the only way to cure periampullary neoplasms, or at least prolongs survival, age should never be the sole contraindication to surgery.

METHODS

Study selection

A systematic review of the literature was performed using the Medline, Embase and Cochrane databases to identify all eligible studies that compared patients undergoing PD for periampullary tumors in terms of age. The used search terms included: "pancreatoduodenectomy", "pancreaticoduodenectomy", "Whipple", "Traverso", "pancreatic head resection", "pancreatic head tumour", "duodenopancreatectomy", "older", "elderly", "octagenarian", "nonagenarian", "septuagenarian", "age", "70", "75", "80" and "65". These terms were combined using Boolean operators "AND" and "OR". Some references of the acquired articles were also

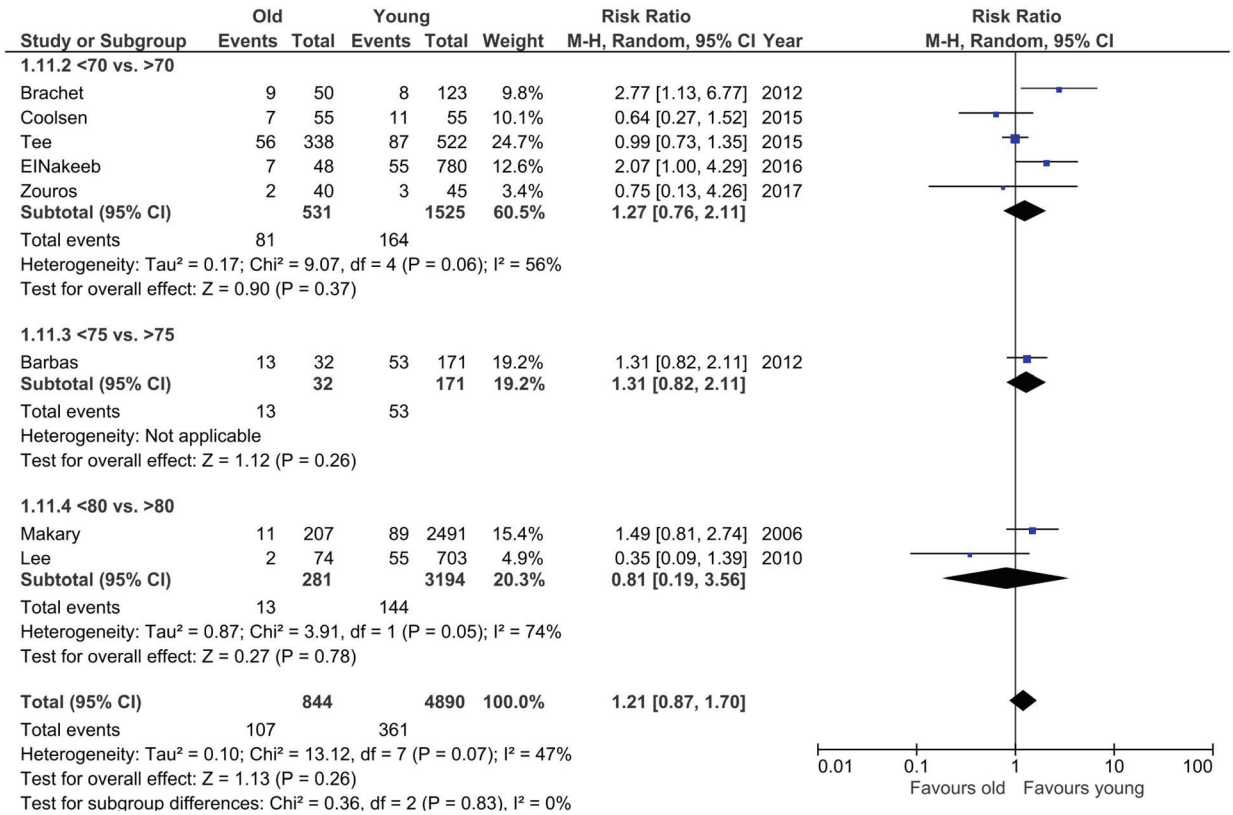

Figure 13: Pooled estimates of readmissions comparing elderly population vs. younger population. CI confidence interval, df degrees of freedom.

located manually. The most recent search was performed on 10th of April, 2017. Ovid search strategy is available in supplementary Figure 2.

Studies eligible for further analysis had to fulfill the following criteria: (1) a comparison of the characteristics and perioperative outcomes of older patients vs. younger patients undergoing pancreatoduodenectomy; (2) an objective evaluation of mortality or overall morbidity; (3) publication in English. Studies were excluded when there was: (1) a lack of comparative data; (2) a lack of primary outcomes or insufficient data to analyze; (3) a focus on procedures other than pancreatoduodenectomy; or (4) an extraction of data specifically concerning pancreatoduodenectomy was not possible.

Outcomes of interest

Older patients were compared with younger patients on the basis of postoperative complications, oncologic safety (R0 rate), and length of hospital stay (LOS). All-cause mortality was defined as the number of deaths during the longest follow-up period. Overall morbidity was defined as the number of patients with at least one complication during the longest follow-up period. Complications included pancreatic fistula, delayed gastric emptying (DGE), postoperative hemorrhage, bile leakage, surgical site infection (SSI), pulmonary complications, and cardiovascular complications.

Data extraction and quality assessment

All references were reviewed and evaluated by three teams of two researchers. In case of any doubts about eligibility for inclusion, an attempt was made to reach consensus within the group. If no resolution was possible, an arbitrary decision was made by another reviewer. Data from the included studies were extracted independently by all teams. Only full-length articles were eligible for extraction. When available, the following data was extracted: first author, year of publication, number of operated subjects, type of surgery, age cut-off point, and short-term outcomes.

Non-randomized studies were evaluated according to the Newcastle–Ottawa Scale (NOS), which consists of three factors: patient selections, comparability of study groups, and assessment of outcomes. A score of 0 to 9 was assigned to each study and studies achieving a score of 6 or higher were considered high-quality. This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) consensus statement. The study was registered in the PROSPERO Database and the assigned number is CRD42017070692.

Data analysis

Analysis was performed using RevMan 5.3 (freeware from The Cochrane Collaboration). Statistical heterogeneity and inconsistency were measured using Cochran's Q tests and I2, respectively. Qualitative outcomes from individual studies were analyzed to assess individual and pooled risk ratios (RR) with 95% confidence intervals (CI) favoring older populations undergoing pancreatoduodenectomy, and by using the Mantel-Haenszel random-effects method. For positive outcomes, RR was calculated for "non-event" occurrence. When appropriate, mean and standard deviation were calculated from medians and interquartile ranges using a method proposed by Hozo *et al.* [76]. Weighted mean differences (WMD) with a 95% CI are presented for quantitative variables using the inverse variance random-effects method. Statistical significance was observed with a two-tailed 0.05 level for hypotheses and with 0.10 for heterogeneity testing, while unadjusted p-values were reported accordingly. Each analysis involved subgroup analysis with cut-off points set at 65, 70, 75, and 80 years old. For studies that reported more than two age groups, only qualitative outcomes were analyzed (3 groups were divided into 2 to provide a dichotomous outcome, e.g. groups <70 vs. 71–80 vs. >80 were transformed to <80 vs. >80).

Abbreviations

PD: pancreatoduodenectomy; WMD: Weighted mean differences; RR: risk ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE: Meta-Analysis of Observational Studies in Epidemiology; NOS: Newcastle–Ottawa Scale; SSI: surgical site infection ; DGE: delayed gastric emptying ; LOS: length of stay.

Author contributions

Michał Pędziwiatr–idea conception, manuscript preparation, screening and data extraction, data interpretation, final revision of the manuscript; Piotr Małczak–screening supervisor, extraction supervisor, data synthesis, figure and table preparation, data interpretation

Magdalena Mizera–screening and data extraction, data interpretation' Jan Witowski - screening and data extraction, data interpretation; Grzegorz Torbicz - screening and data extraction; Piotr Major - screening and data extraction; Magdalena Pisarska - screening supervisor, extraction supervisor, data synthesis; Michał Wysocki–figure and table preparation; Miłosz Jankowski–data interpretation; Mateusz Rubinkiewicz - data interpretation, screening and data extraction; Anna Lasek–language correction; Jan Kulawik–manuscript preparation, screening and data extraction; Andrzej Budzyński–final revision of the manuscript.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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