

# Survival and complications of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in elderly patients: a systematic review and meta-analysis

J. TAO<sup>1</sup>, P.-T. JI<sup>1</sup>, J.-J. SHEN<sup>2</sup>, Y. LU<sup>1</sup>

<sup>1</sup>Department of Interventional Radiotherapy, Huzhou Cent Hospital, Affiliated Cent Hospital HuZhou University, Zhejiang Province, P.R. China

<sup>2</sup>Department of Oncology, Huzhou Cent Hospital, Affiliated Cent Hospital HuZhou University, Zhejiang Province, P.R. China

**Abstract.** – **OBJECTIVE:** Peritoneal cancer is an uncommon form of terminal malignancy with substantial morbidity and mortality. While both young and elderly population groups with peritoneal cancer are treated by joint cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, studies suggest that they might have a differential prognostic outcome in terms of postoperative morbidity and mortality. To date, only one review has attempted to evaluate the comparative impact of postoperative complications and overall mortality in these age groups. However, a recent publication of several high-quality cohort trials needs an update of the existing consensus. To compare the impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on postoperative complications and overall mortality in younger and elderly population groups.

**MATERIALS AND METHODS:** A systematic search of the academic literature was performed according to the PRISMA guidelines across five databases: Web of Science, EMBASE, CENTRAL, Scopus, and MEDLINE. A random-effect meta-analysis was conducted to evaluate the comparative outcomes between the impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on postoperative complications and overall mortality in younger and elderly population groups.

**RESULTS:** From 963 studies, 16 eligible studies that evaluated the comparative outcomes of morbidity and mortality between 3067 young and 878 elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were included. A meta-analysis revealed higher risks of postoperative complications (Odds ratio: 1.18, 95% C.I.: 0.90 to 1.55) and overall mortality (3.28, 1.93 to 5.5) for elderly patients as compared to the younger patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. There were no differences in risks of the onset of anastomotic leakage

(1.0, 0.47 to 2.14) and duration of hospital stay (Hedge's g: 0.02, -0.08 to 0.14) between elderly and younger patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

**CONCLUSIONS:** The study provides updated evidence regarding poor postoperative morbidity and mortality outcomes in elderly patients as compared to younger patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and may help clinicians to better stratify the risks associated with the conventional management of peritoneal carcinoma in elderly population groups.

*Key Words:*

Hyperthermic intraperitoneal chemotherapy, Cytoreductive surgery, Aging, complications, Mortality.

## Introduction

Peritoneal cancer is an uncommon form of terminal malignancy<sup>1,2</sup>. According to the National Cancer Institute, the onset of peritoneal malignancy starts by direct invasion of free cancer cells in the serosa and stomata lining of the peritoneum (i.e., that covers the abdominal cavity) either on its own or from the adjoining gastrointestinal, gynecological organs<sup>3,4</sup>. Epidemiological studies have reported that peritoneal cancer occurs with an incidence rate of around 3% to 7%<sup>5,6</sup>, and is associated with a high mortality rate<sup>7,8</sup>.

Typical management of peritoneal cancer involves cytoreductive surgery alongside hyperthermic intraperitoneal chemotherapy as standardized means of treatment<sup>2,9,10</sup>. However, recent studies have suggested that while these radical procedures might be beneficial for younger population groups, they are not as effective

for elderly patients<sup>9,11,12</sup>. Studies have reported that elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy exhibit high postoperative morbidity (i.e., 20 to 80%) and mortality rates (i.e., 3% to 28%) as compared to their younger counterparts (i.e. morbidity: 12% to 25 %, mortality 1% to 5%)<sup>13-17</sup>. It is possible that increased risks of postoperative complications and overall mortality in elderly population groups are caused by the aggressive nature of the cytoreductive surgery and the chemotoxicity of chemotherapeutic drugs<sup>2</sup>.

To date, several cohort studies have attempted to compare the postoperative morbidity and mortality-related outcomes between young and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy<sup>11,12,16,18-21</sup>. These studies report a lack of consensus regarding the impact of aging on postoperative complications in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. While some studies report lower rates<sup>18,19</sup>, or no differences<sup>16,22</sup> in the rate of postoperative complications in younger patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, other studies show comparatively higher events of postoperative complications in elderly patients<sup>12,15,21,23,24</sup>. Similarly, there is a lack of consensus regarding postoperative mortality between younger and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. While some studies had reported a stronger negative influence on postoperative mortality in elderly patients<sup>11,12,15,20,21,24,25</sup>, others had reported a negligible difference between younger and elderly cohorts<sup>23,26</sup>.

To the best of our knowledge, only one separate review study has attempted to evaluate the postoperative morbidity, and mortality-related impact between elderly and young patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy<sup>9</sup>. However, since the publication of this review, several high-quality retrospective cohort studies have been published that too have evaluated the comparative outcome of postoperative complications and mortality between elderly and young patients<sup>11,12,16,20</sup>. The aim of this systematic review and meta-analysis is to summarize the current state of evidence regarding the risks of postoperative complications and mortality between elderly and young patients undergoing cytore-

ductive surgery and hyperthermic intraperitoneal chemotherapy. These findings will help to deduce best practice guidelines (i.e., preoperative and postoperative), especially for nursing professionals, and surgeons, for effective reduction morbidity and mortality-related outcomes in elderly patients with peritoneal cancer undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

## Materials and Methods

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher, Liberati, Tetzlaff, Altman, & The, 2009) for performing this meta-analysis.

### Data Search Strategy

The literature search was performed in five scientific databases (Web of Science, MEDLINE, CENTRAL, EMBASE, and Scopus) from inception till April 2021 using a combination of MeSH keywords including “hyperthermic intraperitoneal chemotherapy”, “HIPEC”, “cytoreductive surgery”, “elderly”, “young”, “complications”, “postoperative complications”, and “mortality”. Additional relevant studies were identified by manual search of bibliography sections of the included studies. The inclusion criteria were as follows:

1. Studies reporting comparative outcomes of postoperative complications and mortality between elderly and young patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.
2. Studies of human participants.
3. Case-control studies, prospective cohort trials, or retrospective cohort trials.
4. Studies published in peer-reviewed scientific journals.
5. Studies published in English.

Screening was performed by two independent reviewers, and cases of disagreements were resolved by discussions with a third independent reviewer.

### Quality Assessment

Risk of bias in the included studies was appraised using the Newcastle Ottawa scale<sup>27</sup>. This tool evaluates the outcomes for selective report-

ing, confounding bias, measurement of outcomes, and incomplete data availability as threats that can instigate instigating. Methodological quality was independently assessed by two reviewers, and cases of disagreements were resolved by discussions with a third independent reviewer.

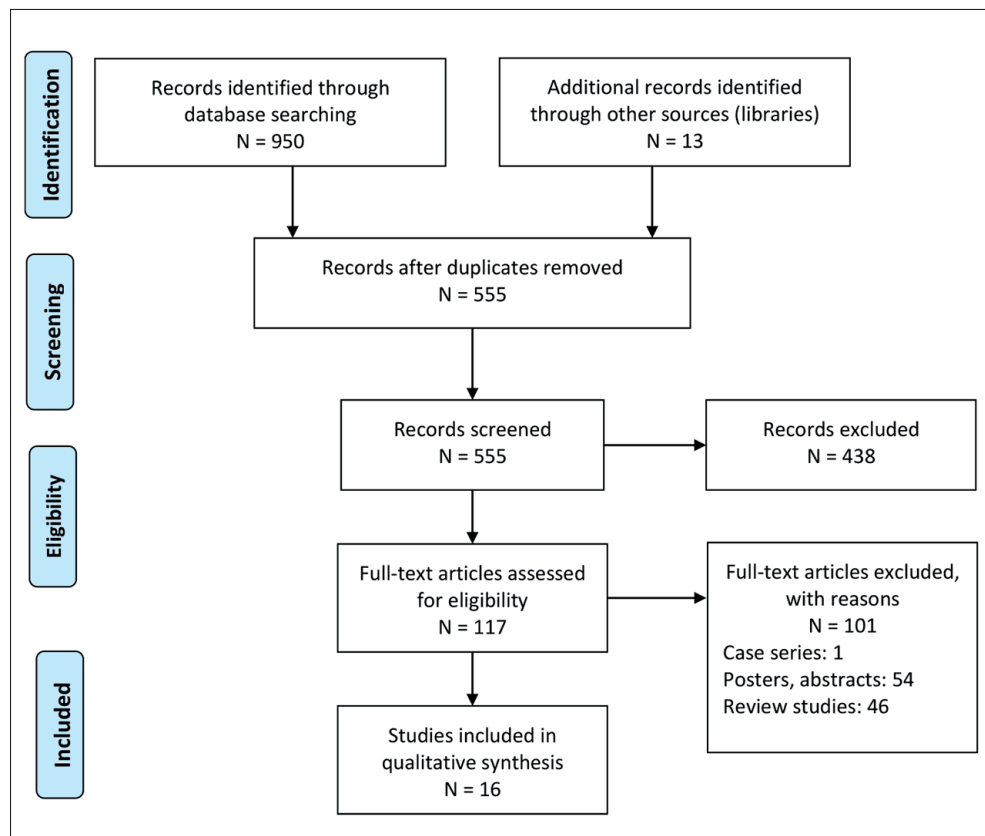
**Data Analysis**

A within-group meta-analysis was performed using CMA, Comprehensive Meta-analysis version 2.0<sup>28</sup> based on the random-effects model<sup>29</sup>. Odds ratio was calculated to evaluate the postoperative complications ( $\geq$  grade 3 Clavien Dindo classification) and mortality between elderly and young patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Subgroup analyses were carried out to compare the outcomes between studies reporting different cut-off ages to segregate their young and elderly sample. Heterogeneity among the studies was assessed by  $I^2$  statistics.  $I^2$  between 0-25% was considered indicative of negligible heterogeneity, 25%-75% - of mod-

erate heterogeneity, and  $\geq 75\%$  - of substantial heterogeneity<sup>30</sup>. The method of Hozo et al<sup>31</sup> was used for the studies that provided the descriptive statistics as median and range to convert it into mean and standard deviation. Publication bias was evaluated by Duval and Tweedy’s trim and fill procedure<sup>2</sup> that imputes studies from either side of the plotted graph to identify any unbiased effect. The significance level was determined at 5% for this study.

**Results**

A search across five academic databases provided a total of 950 studies. Additional 13 studies were identified during the screening of the reference sections of the included studies. A total of 16 studies met the inclusion criteria (Figure 1). All of the included studies were retrospective cohort studies<sup>11,12,15,16,18-26,30-32</sup>. The data were extracted in a tabular format and summarized in Table I.



**Figure 1.** Illustrating the PRISMA flowchart.

**Table I.** Demonstrates the details of the included studies.

Study	Country	Type of study	Sample descriptive	Primary tumor	Anastomosis	Complications	Description of complications	Hospital stay (days)	Mortality (n)
Keyes et al. (2021)	UK	Retrospective cohort study	< 65: 53 ≥ 65: 69	< 65: Multiple ≥ 65: Multiple	< 65: 3 ≥ 65: 1	< 65: 19 ≥ 65: 14	Hemorrhage, anastomotic leak, bowel obstruction, venous thromboembolism, pulmonary embolism, sepsis, surgical site infection	< 65: 13 ≥ 65: 14.5	< 65: 1 ≥ 65: 0
Zhou et al. (2021)	China	Retrospective cohort study	< 65: 75 (35F, 40M) ≥ 65: 25 (12F, 13M)	< 65: Colorectal ≥ 65: Colorectal	< 65: 2 ≥ 65: 1	< 65: 15 ≥ 65: 7	Arrhythmia, pneumonia, pleural effusion, anastomotic leakage, gastrointestinal hemorrhage, renal failure, urinary retention, abdominal abscess, rectovaginal fistula, wound infection, intraabdominal hemorrhage	< 65: 14.8 ± 5.1 ≥ 65: 19.2 ± 7.4	< 65: 0 ≥ 65: 0
Zambrano-Vera et al. (2021)	USA	Retrospective cohort study	< 65: 28 ≥ 65: 14	< 65: Multiple ≥ 65: Multiple	-	< 65: 9 ≥ 65: 7	Abdominal seroma, abdominal abscess, wound dehiscence, wound infection, pancreatic leak, pancreatic fistula, gastric perforation, intestinal fistula, bowel leak, ureteral leak, intraabdominal bleeding, supraventricular tachycardia, cardiac arrest, hypotension, pulmonary embolism, stroke, acute respiratory distress syndrome	< 65: 10 ≥ 65: 13	< 65: 0 ≥ 65: 5
Ezzedine et al. (2021)	France	Retrospective cohort study	< 65: 65 (31F, 34M) ≥ 65: 30 (15F, 15M)	≥ 65: Multiple < 65: Multiple	< 65: 9 ≥ 65: 2	< 65: 18 ≥ 65: 6	Hemorrhage, tumor perforation, intestinal injury, diaphragmatic breach	< 65: 26.7 ± 19.4 ≥ 65: 22.4 ± 10.3	< 65: 0 ≥ 65: 4
Turgeon et al. (2020)	USA	Retrospective cohort study	< 65: 850 (527F, 323M) ≥ 65: 240 (119M, 121M)	< 65: Multiple ≥ 65: Multiple	-	< 65: 152 ≥ 65: 55	-	-	< 65: 6 ≥ 65: 6

*Continued*

**Table I (Continued).** Demonstrates the details of the included studies.

Study	Country	Type of study	Sample descriptive	Primary tumor	Anastomosis	Complications	Description of complications	Hospital stay (days)	Mortality (n)
Oemrawsingh et al. (2019)	Netherlands	Retrospective cohort study	< 65: 77 (40F, 37M) ≥ 65: 45 (24F, 21M)	< 65: Multiple ≥ 65: Multiple	< 65: 4 ≥ 65: 2	< 65: 8 ≥ 65: 12	Anastomotic leakage, intra-abdominal bleeding, abscess, wound infection, wound dehiscence, pneumonia, pulmonary embolism, urinary tract infection	< 65: 18 ≥ 65: 17	< 65: 1 ≥ 65: 4
Naffouje and Salti (2018)	USA	Retrospective cohort study	< 65: 24 (17F, 11M) ≥ 65: 69 (38F, 31M)	< 65: Multiple ≥ 65: Multiple	-	< 65: 4 ≥ 65: 5	-	<65: 11.17 ± 6.37 ≥ 65: 11.35 ± 6.3	< 65: 0 ≥ 65: 3
Arslan et al. (2018)	Turkey	Retrospective cohort study	< 65: 69 (38F, 31M) ≥ 65: 31 (18F, 13M)	< 65: 1 Colorecta ≥ 65: Colorectal	< 65: 45 ≥ 65: 25	< 65: 23 ≥ 65: 9	-	< 65: 17 ± 11.8 ≥ 65: 16.8 ± 14.3	<65: 5 ≥ 65: 4
Wong et al. (2018)	Singapore	Retrospective cohort study	< 65: 159 (121F, 38M) ≥ 65: 18 (12F, 6M)	< 65: Multiple ≥ 65: Multiple	< 65: 1 ≥ 65: 2	< 65: 45 ≥ 65: 6	Pneumonia, pneumothorax, postoperative ileus, surgical site infection, bleeding, urinary tract infection, deep vein thrombosis, fever, chemical peritonitis, increase serum creatinine, burst abdomen, fistula formation, perforation of viscera	< 65: 14 ≥ 65: 13.5	< 65: 1 ≥ 65: 2
Kitai et al. (2017)	Japan	Retrospective cohort study	< 70: 28 (18F, 10M) ≥ 70: 14 (7F, 7M)	< 70: - ≥ 70: Multiple	< 70: 1 ≥ 70: 1	< 70: 6 ≥ 70: 7	Anastomotic leakage, peritonitis, bleeding, respiratory failure	-	< 70: 0 ≥ 70: 2

*Continued*

**Table I (Continued).** Demonstrates the details of the included studies.

Study	Country	Type of study	Sample descriptive	Primary tumor	Anastomosis	Complications	Description of complications	Hospital stay (days)	Mortality (n)
Alyami et al. (2016)	France	Retrospective cohort study	< 70: 704 (503F, 201M) ≥70: 188 (122F, 66M)	< 70: Multiple ≥ 70: Multiple	-	< 70: 270 ≥ 70: 77	Intraabdominal abscess, digestive fistula, intraabdominal bleeding, incisional dehiscence, wound infection, anemia, deep vein thrombosis, cardiac arrhythmia, digestive arterial thrombosis, pancreatitis, anorexia, acute respiratory distress syndrome, renal insufficiency and need for dialysis	< 70: 20 ≥ 70: 20	< 70: 19 ≥ 70: 10
Beckert et al. (2015)	Germany	Retrospective cohort study	< 70: 352 (130F, 222M) ≥70: 29 (7F, 22M)	< 70: Multiple ≥ 70: Multiple	< 70: 11 ≥ 70: 0	< 70: 163 ≥ 70: 22	Fever, anastomotic failure, surgical site infection, burst abdomen, pancreatic fistula, pulmonary embolism, pneumonia, pleural effusion, small bowel fistula, biliary leakage, deep vein thrombosis, increase in serum creatinine, HIPEC associated leucopenia	-	< 70: 19 ≥ 70: 1
Y. Huang et al. (2015)	Australia	Retrospective cohort study	< 65: 487 (289F, 198M) ≥ 65: 124 (60F, 64M)	< 65: Multiple ≥ 65: Multiple	-	< 65: 214 ≥ 65: 49	-	< 65: 22.5 ≥ 65: 22	< 65: 10 ≥ 65: 4

Continued

**Table 1 (Continued).** Demonstrates the details of the included studies.

Study	Country	Type of study	Sample descriptive	Primary tumor	Anastomosis	Complications	Description of complications	Hospital stay (days)	Mortality (n)
Spiliotis et al. (2014)	Greece	Retrospective cohort study	< 70: 70 ≥ 70: 30	< 70: Multiple ≥ 70: Multiple	-	< 70: 29 ≥ 70: 15	Pulmonary embolism, hypertension, atrial fibrillation, pneumonia, leukopenia, prolonged ileus, urinary tract infection, haemorrhage, peritonitis, pancreatic fistula, drainage of intraabdominal collection	-	< 70: 1 ≥ 70: 1
Tabrizian et al. (2013)	USA	Retrospective cohort study	≤ 65: 135 (77F, 58M) ≥ 65: 35 (17F, 18M)	< 65: Multiple ≥ 65: Multiple	< 65: 85 ≥ 65: 16	< 65: 29 ≥ 65: 6	Intraabdominal abscess, wound infection, intraabdominal leak, abscess, pulmonary embolism, deep vein thrombosis, respiratory failure, bleeding	< 65: 11.7 ± 15.5 ≥ 65: 12.6 ± 15.8	< 65: 4 ≥ 65: 8
Macri et al. (2011)	Italy	Retrospective cohort study	≤ 65: 19 ≥ 65: 11	< 65: Multiple ≥ 65: Multiple	-	< 65: 4 ≥ 65: 3	Intestinal fistula, anastomotic leakage, bowel perforation	< 65: 19.1 ≥ 65: 15.6	< 65: 1 ≥ 65: 2

M: Mean; S.D: Standard deviation, F: Female, M: Male, HIPEC: Hyperthermic intraperitoneal chemotherapy.

### **Participant Information**

Data from 3945 (2230F, 1547M) patients were included in the 16 studies. Of them, 3067 (1791F, 1163M) patients were in the young group, and 878 (439F, 384M) patients were in the old group. Four studies did not report the gender distribution of their sample<sup>12,25,26,3</sup>. In the included sample the age distribution was provided in two different manners: 12 studies had reported the age cut-off between younger and elderly participants at 65 years<sup>11,12,15,16,18-21,25,33-35</sup> and 4 studies had reported the cut-off at 70 years<sup>22,23,24,26</sup>.

### **Quality Assessment for Cohort Studies**

Risk of bias in the methodology of the cohort studies was assessed using the Newcastle Ottawa scale (Table II), and the overall risk was found to be low in all the included studies (Figure 2).

### **Publication Bias**

Duval and Tweedy's trim and fill method were used to determine missing studies according to the random effect model on either side of the mean effect of the funnel plot. As shown in Figure 3, one study was missing on the left side of the mean effect. After using trim and fill, the imputed point estimates and the 95% confidence interval were 1.18 (0.90 to 1.55) for the included studies based on the overall random effect models. The publication bias is reported in Figure 3.

### **Meta-Analysis Report**

Postoperative complications ( $\geq$  grade 3 Clavien Dindo classification).

The outcome of overall survival was reported by 16 studies. We observed an increased odds ratio suggestive of increased risks of postoperative complication for elderly patients as compared to the younger patients (Figure 4) (Odds ratio: 1.18, 95% C.I: 0.90 to 1.55,  $p=0.21$ ), with negligible heterogeneity ( $I^2$ : 15.4%). In addition, subgroup analysis was performed with separate comparative evaluation for studies reporting the cut-off age at 65 and 70 years.

#### **65-Year Cut-Off**

The outcome of postoperative complications in elderly ( $\geq 65$  years) and younger ( $< 65$  years) patients were reported by 12 studies. We observed a marginally reduced odds ratio suggesting increased risks of postoperative complications in

younger patients as compared to the older patients (Figure 5) (Odds ratio: 1.02, 95% C.I: 0.75 to 1.38,  $p=0.88$ ), with negligible heterogeneity ( $I^2$ : 2.4%).

#### **70-Year Cut-Off**

The outcome of postoperative complications of elderly ( $\geq 70$  years) and younger ( $< 70$  years) patients were reported by four studies. We observed a higher odds ratio suggesting increased risks of postoperative complications in older patients as compared to the younger patients (Figure 6) (Odds ratio: 2.37, 95% C.I: 0.99 to 5.67,  $p=0.052$ ), with moderate heterogeneity ( $I^2$ : 27.06%).

### **Mortality**

The outcome of overall survival was reported by 15 studies. We observed an increased odds ratio suggesting higher risks of mortality for elderly patients as compared to younger patients (Odds ratio: 3.28, 95% C.I: 1.93 to 5.58,  $p<0.001$ ), with negligible heterogeneity ( $I^2$ : 3.1%) (Figure 7). We next performed subgroup analysis in which separate comparative evaluation of mortality was done for studies reporting the cut-off age at 65 and 70 years.

#### **65-Year Cut-Off**

The outcome of mortality of elderly ( $\geq 65$  years) and younger ( $< 65$  years) patients was reported by eleven studies. We observed a reduced odds ratio suggesting increased risks of mortality in elderly patients as compared to the younger patients (Figure 8) (Odds ratio: 4.1, 95% C.I: 2.16 to 8.01,  $p<0.001$ ), with negligible heterogeneity ( $I^2$ : 2.06%).

#### **70-Year Cut-Off**

The outcome of mortality in elderly ( $\geq 70$  years) and younger ( $< 70$  years) patients were reported by four studies. We observed a higher odds ratio for the elderly group suggesting increased risks of mortality in elderly patients as compared to the younger patients (Figure 9) (Odds ratio: 1.94, 95% C.I: 0.97 to 3.88,  $p=0.058$ ), with no heterogeneity ( $I^2$ : 0%).

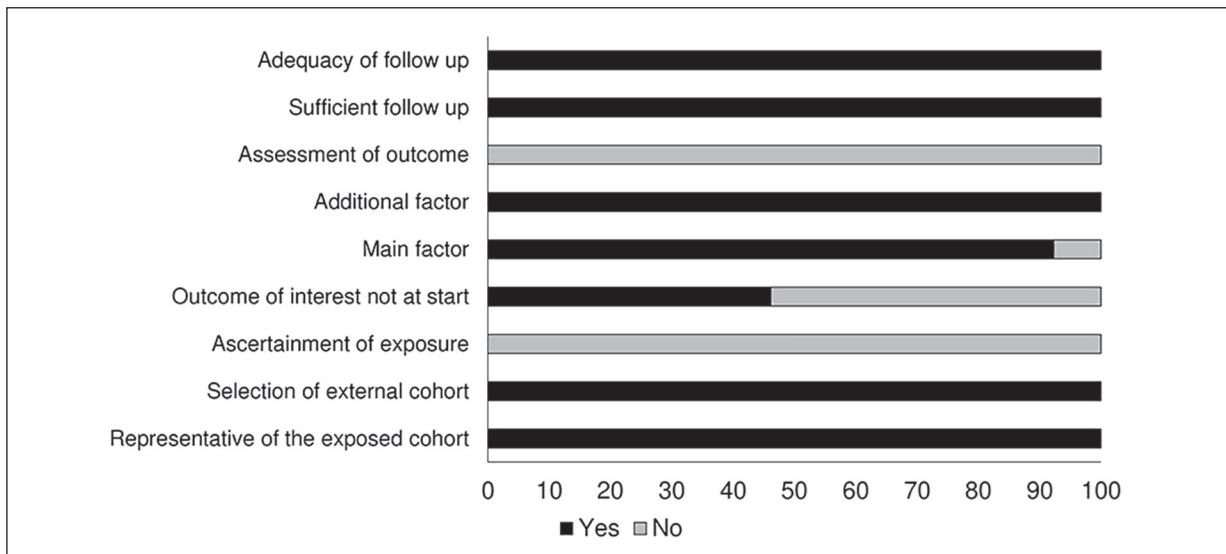
### **Anastomotic Leakage**

The outcome of anastomotic leakage was reported by nine studies. We observed an odds ratio of 1.006 suggesting negligible risks of anas-



**Table II.** Risk of bias for individual studies based on the Newcastle Ottawa scale.

Study	Selection			Comparability			Outcome			Total (9/9)
	Representative of the exposed cohort	Selection of external cohort	Ascertainment of exposure	Outcome of interest does not present at start	Main factor	Additional factor	Assessment of outcome	Sufficient follow up	Adequacy of follow up	
Keyes et al. (2021)	+	+	0	+	+	+	0	+	+	7
Zhou et al. (2021)	+	+	0	+	+	+	0	+	+	7
Zambrano-Vera et al. (2021)	+	+	0	+	+	+	0	+	+	7
Ezzedine et al. (2021)	+	+	0	+	+	+	0	+	+	7
Turgeon et al. (2020)	+	+	0	0	+	+	0	+	+	6
Oemrawsingh et al. (2019)	+	+	0	+	+	+	0	+	+	7
Naffouje and Salti (2018)	+	+	0	+	+	+	0	+	+	7
Arslan et al. (2018)	+	+	0	+	+	+	0	+	+	7
Wong et al. (2018)	+	+	0	0	+	+	0	+	+	6
Kitai et al. (2017)	+	+	0	0	+	+	0	+	+	6
Alyami et al. (2016)	+	+	0	0	0	+	0	+	+	5
Beckert et al. (2015)	+	+	0	0	+	+	0	+	+	6
Y. Huang et al. (2015)	+	+	0	+	+	+	0	+	+	7
Spiliotis et al. (2014)	+	+	0	0	+	+	0	+	+	6
Tabrizian et al. (2013)	+	+	0	+	+	+	0	+	+	7
Macri et al. (2011)	+	+	0	0	+	+	0	+	+	6



**Figure 2.** Demonstrates the risk of bias according to the Newcastle Ottawa scale for cohort studies.

tomotic leakage for elderly patients as compared to the younger patients (Figure 10) (95% C.I: 0.47 to 2.1,  $p=0.98$ ), with no heterogeneity ( $I^2$ : 0%). In addition, we also performed subgroup analysis in which separate comparative evaluation was performed for studies reporting the cut-off age at 65 and 70 years.

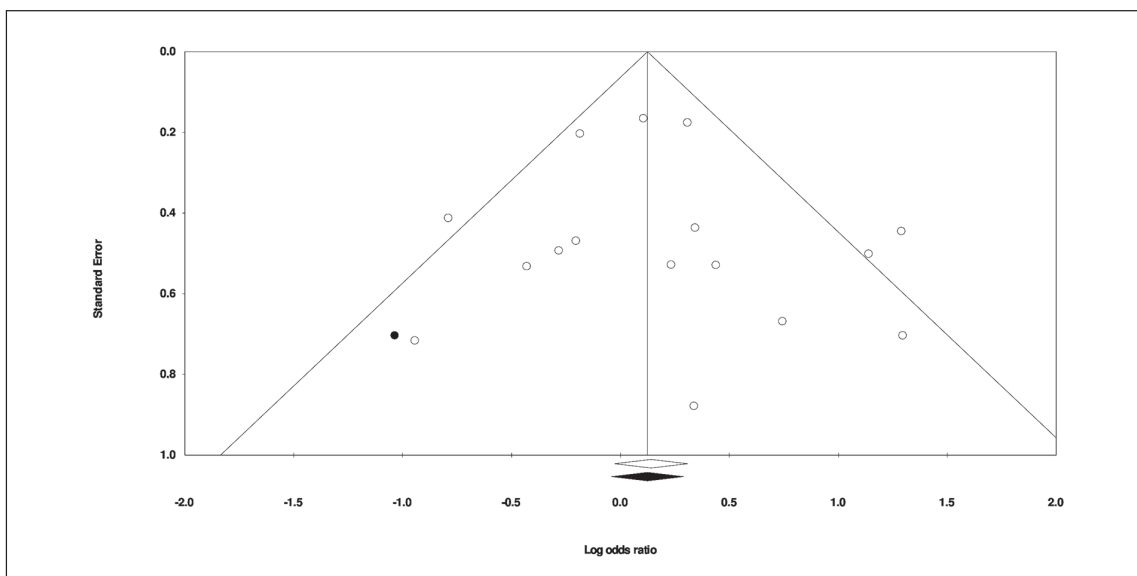
**65-Year Cut-Off**

The outcome of anastomotic leakage between elderly ( $\geq 65$  years) and younger ( $< 65$  years) pa-

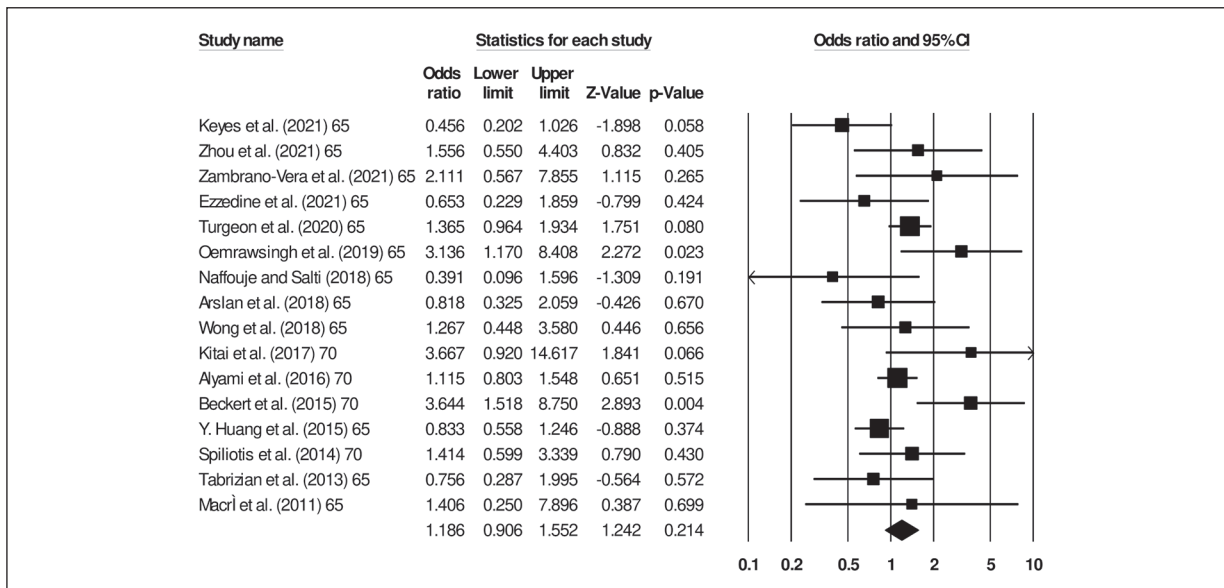
tients were reported by seven studies. We observed an odds ratio of 1.02 suggesting no risks of anastomotic leakage in elderly patients as compared to the younger patients (Figure 11) (95% C.I: 0.42 to 2.45,  $p=0.96$ ), with negligible heterogeneity ( $I^2$ : 10.5%).

**70-Year Cut-Off**

The outcome of anastomotic leakage in elderly ( $\geq 70$  years) and younger ( $< 70$  years) patients were reported by two studies, with a ratio of 1.02, sug-



**Figure 3.** Demonstrates the publication bias by Duval & Tweedy's trim and fill method.

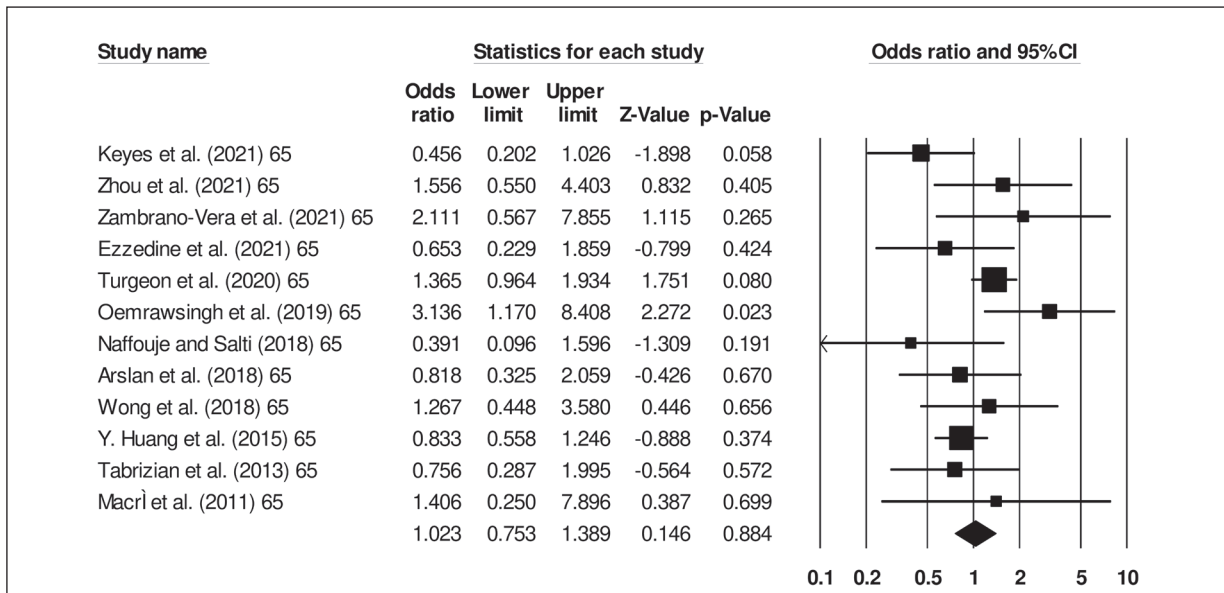


**Figure 4.** Demonstrates the forest plot for studies comparing postoperative complications between young and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of postoperative complications for the elderly group, a lower odds ratio represents higher risks of postoperative complications for the younger group (65: 65 years cut-off, 70: 70 years cut-off).

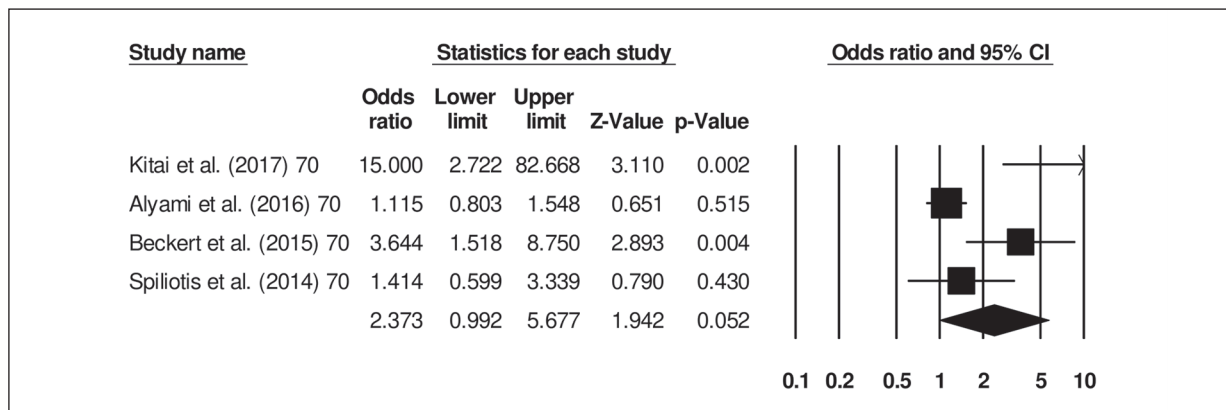
gestive of no increased risk of anastomotic leakage in elderly patients as compared to younger patients (Figure 12) (95% C.I: 0.13 to 7.7,  $p=0.98$ ), with no heterogeneity ( $I^2: 0\%$ ).

#### Duration of Hospital Stay

The duration of hospital stay was reported by 12 studies. There was a *small* positive effect size suggesting negligible differences in the duration



**Figure 5.** Demonstrates the forest plot for studies comparing postoperative complications between young (<65 years) and elderly (≥65 years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of postoperative complications for the elderly (≥65 years) group, a lower odds ratio represents higher risks of postoperative complications for the younger (<65 years) group (65: 65 years cut-off, 70: 70 years cut-off).

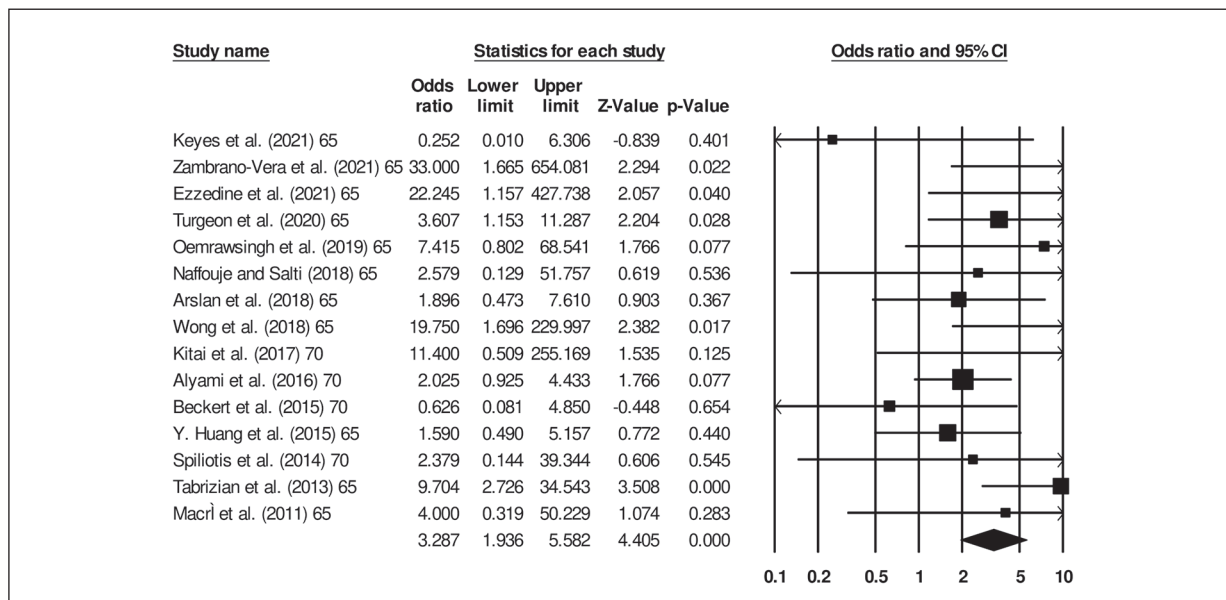


**Figure 6.** Demonstrates the forest plot for studies comparing postoperative complications between young (<70 years) and elderly (≥70 years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of postoperative complications for the elderly (≥70 years) group, a lower odds ratio represents higher risks of postoperative complications for the younger (<70 years) group (65: 65 years cut-off, 70: 70 years cut-off).

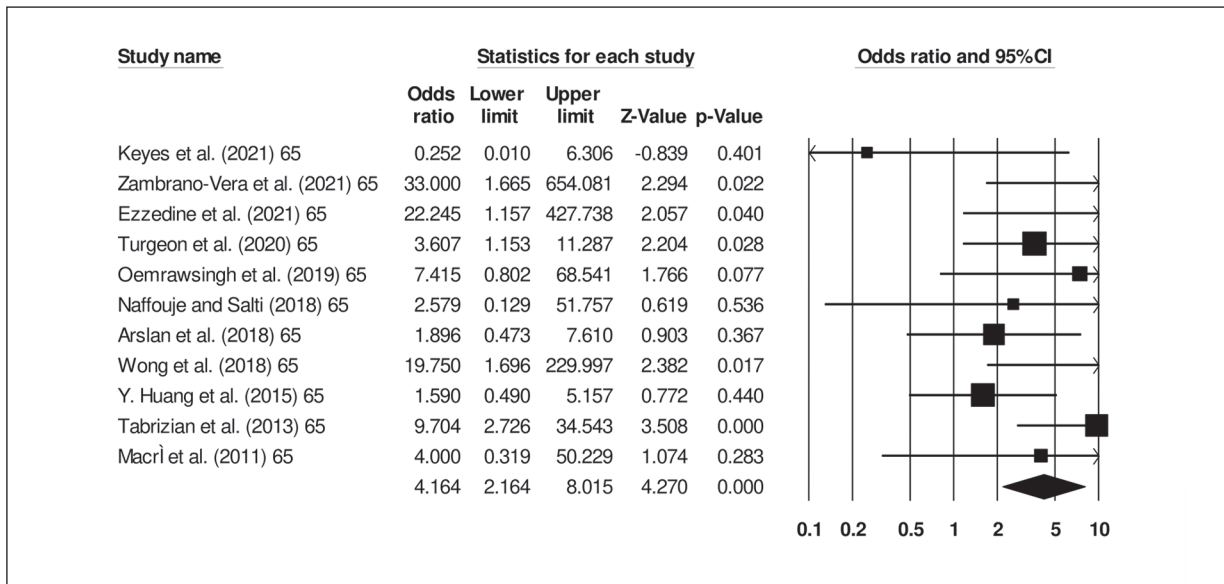
of hospital stay between elderly patients and younger patients (Figure 13) (Hedge’s g: 0.0295% C.I: -0.08 to 0.14, p=0.66), with negligible heterogeneity (I<sup>2</sup>: 8.6%). In addition, we also performed subgroup analysis in which separate comparative evaluation was performed for studies reporting the cut-off age at 65 years (i.e., only one study had evaluated the outcome at 70-year cut-off range).

**65-Year Cut-Off**

The duration of hospital stays in elderly (≥65 years) and younger (<65 years) patients were reported by 11 studies. We observed a *small* positive effect size suggesting negligible differences in the duration of hospital stay between elderly patients and younger patients (Figure 14) (Hedge’s g: 0.03, 95% C.I: -0.10 to 0.18, p=0.60), with negligible heterogeneity (I<sup>2</sup>: 6.2%).



**Figure 7.** Demonstrates the forest plot for studies comparing mortality between young and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of mortality for the elderly group, a lower odds ratio represents higher risks of mortality for the younger group (65: 65 years cut-off, 70: 70 years cut-off).

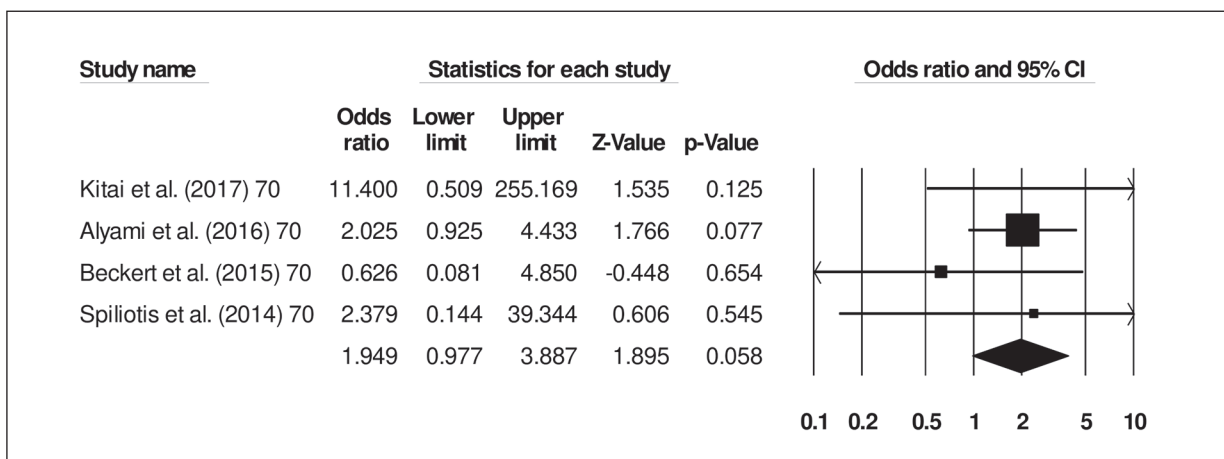


**Figure 8.** Demonstrates the forest plot for studies comparing mortality between young (<65 years) and elderly (≥65 years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents a higher risk of mortality for the elderly (≥65 years) group, a lower odds ratio represents higher risks of mortality for the younger (<65 years) group (65: 65 years cut-off, 70: 70 years cut-off).

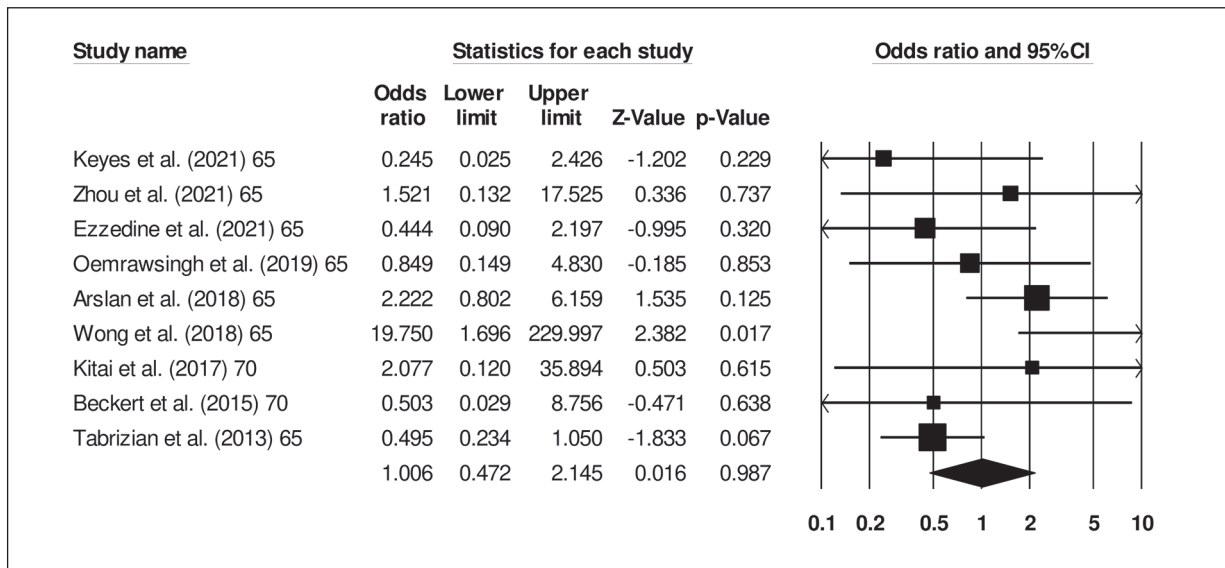
### Discussion

The present systematic review and meta-analysis provides updated evidence regarding postoperative morbidity and mortality outcomes in young and elderly patients undergoing cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy. We report worse outcomes

for elderly patients in terms of postoperative complications and overall mortality as compared to younger patients. In subsequent subgroup analyses, we also report that for both cut-off ages (65 and 70 years) there were higher risks of postoperative complications and mortality for the elderly population groups as compared to younger population groups. No differences



**Figure 9.** Demonstrates the forest plot for studies comparing mortality between young (<70 years) and elderly (≥70 years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of mortality for the elderly (≥70 years) group, a lower odds ratio represents a higher risk of mortality for the younger (<70 years) group (65: 65 years cut-off, 70: 70 years cut-off).

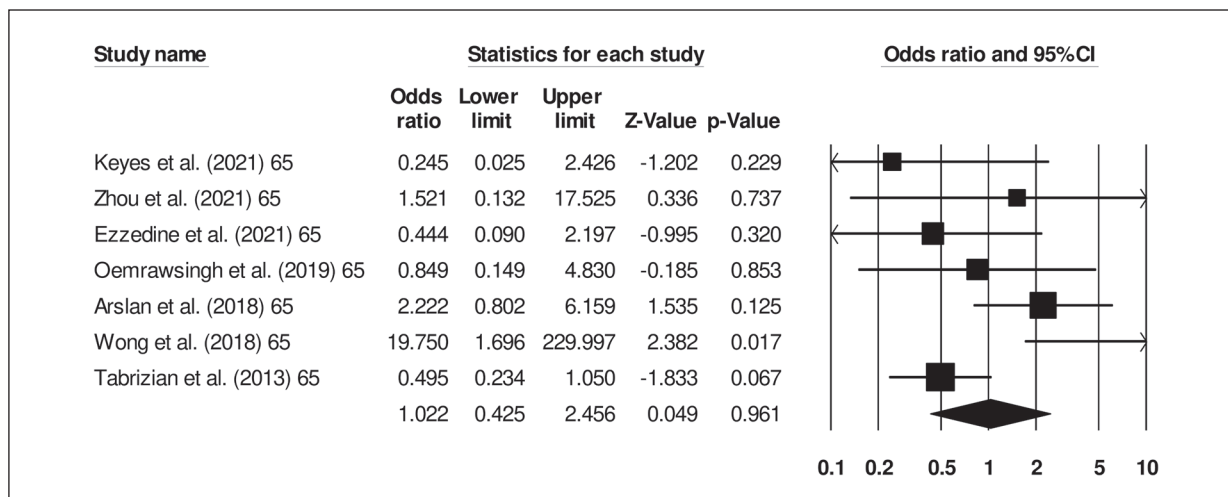


**Figure 10.** Demonstrates the forest plot for studies comparing outcome of anastomotic leakage between young and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of anastomotic leakage for the elderly group, a lower odds ratio represents higher risks of anastomotic leakage for the younger group (65: 65 years cut-off, 70: 70 years cut-off).

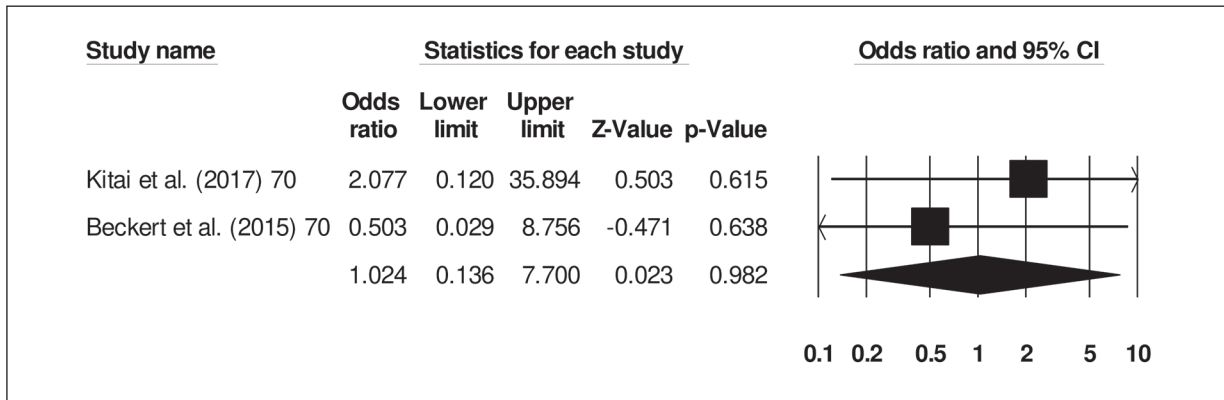
were observed in the incidences of anastomotic leakage and overall duration of hospital stay between two groups.

Management of peritoneal cancer is considered particularly challenging for clinicians, surgeons and nursing professionals because of its poor prognosis, and heterogeneous mani-

festations<sup>36,34</sup>. Patients with peritoneal cancer irrespective of their age, are often treated with a similar approach i.e., cytoreductive surgery and hyperthermic intraperitoneal chemotherapy<sup>10,38,39</sup>. However, recent studies increasingly suggest that while younger patients fare better when subjected to such aggressive interventions,



**Figure 11.** Demonstrates the forest plot for studies comparing outcome of anastomotic leakage between young (<65 years) and elderly (≥65 years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of anastomotic leakage for the elderly group, a lower odds ratio represents higher risks of anastomotic leakage for the younger group (65: 65 years cut-off, 70: 70 years cut-off).

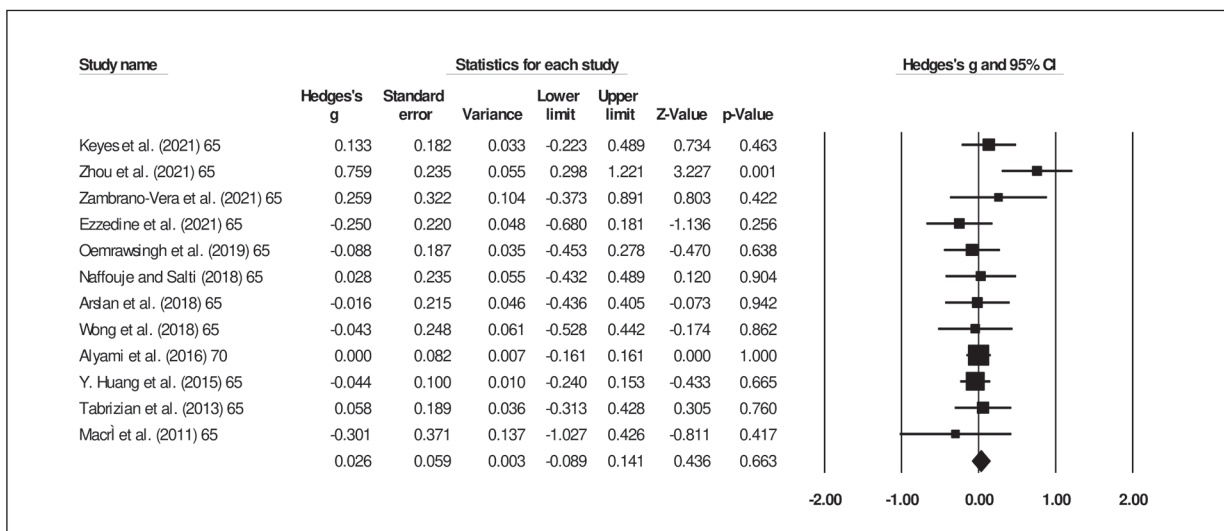


**Figure 12.** Demonstrates the forest plot for studies comparing outcome of anastomotic leakage between young (<70years) and elderly (≥70years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher odds ratio represents higher risks of anastomotic leakage for the elderly group, a lower odds ratio represents higher risks of anastomotic leakage for the younger group (65: 65 years cut-off, 70: 70 years cut-off).

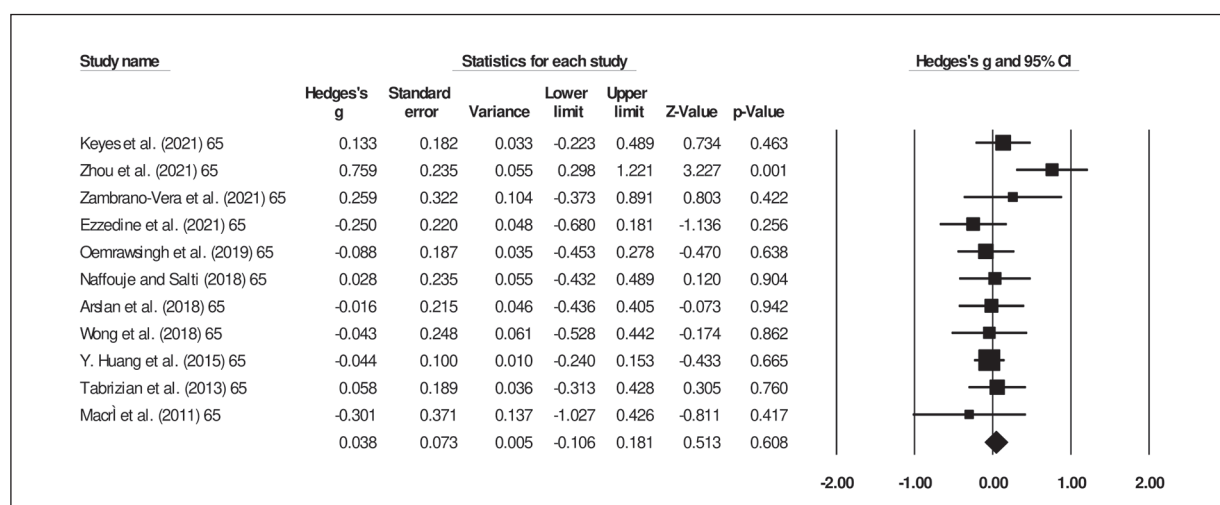
elderly patients often experience higher rates of postoperative complications (i.e. anastomosis leakage, longer duration of hospital stay) and mortality<sup>9,11,12,15,16</sup>.

In the present systematic review, almost all the included studies had reported worse postoperative outcomes in terms of complications for elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as compared to younger patients.

Beckert et al<sup>23</sup> in their study of a cohort representative of the German population, reported higher postoperative complication rates in elderly patients (76%) as compared to younger patients (46%) undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The authors reported that their elderly cohort also exhibited higher Clavien-Dindo grade ≥III level complications as compared to their younger counterparts. The authors sug-



**Figure 13.** Demonstrates the forest plot for studies comparing outcome of duration of hospital stay between young and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The Hedge's g is presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher effect size represents longer duration of hospital stay for the elderly group, a lower effect size represents longer duration of hospital stay for the younger group (65: 65 years cut-off, 70: 70 years cut-off).



**Figure 14.** Demonstrates the forest plot for studies comparing outcome of duration of hospital stay between young (<65 years) and elderly ( $\geq 65$  years) patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The Hedge's g is presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher effect size represents longer duration of hospital stay for the elderly group, a lower effect size represents longer duration of hospital stay for the younger group (65: 65 years cut-off, 70: 70 years cut-off).

gested that the main possible reason behind the higher rates of postoperative complications was the delayed wound healing capabilities of the aged cohort. Similarly, Kitai et al<sup>24</sup> reported significantly higher rates of postoperative complications (i.e., grade 4 to 5) in their elderly cohort as compared to their younger cohort. Here, the authors attributed the higher rates of postoperative complications, especially in terms of respiratory failure in the elderly patients to age-related systemic complications observed pre-operatively in their cohort. The authors also mentioned that because of a higher number of co-existing comorbidities, the elderly patients required longer surgery times as compared to their younger counterparts (surgery time of 676 min for elderly patients versus 607 minutes for young patients), potentially leading to more postoperative complications<sup>40</sup>. In this present meta-analysis, we confirm these findings and report higher risks of postoperative complications (Odds ratio: 1.18) in the elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as compared to their younger counterparts. Moreover, in further subgroup analyses, we also found that studies reporting the cut-off age at 65 (OR: 1.02) and 70 (OR: 2.37) years both detected higher risks of postoperative complications in their elderly cohort. However, there was no significant difference in the rates of

anastomotic leakage (OR: 1.00) and overall duration of hospital stay (g: 0.02) between the two groups. It is possible that a relative difference in terms of the number of studies analyzing these outcomes could be the reason behind this differential outcome. Further studies to elucidate these aspects in greater details are needed.

In the current review we also attempted to develop a consensus regarding the mortality-related outcomes in younger and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. We observed that in the included studies there was a general lack of consensus regarding the mortality-related outcomes in two groups of patients. A retrospective cohort study by Ezzedine et al<sup>11</sup> reported that among 95 patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal metastases, there was significantly higher mortality in elderly patients as compared to younger patients ( $p=0.03$ ). Similarly, Wong et al<sup>21</sup> reported a higher rate of 90-day mortality in their elderly cohort (11.1%) as compared to their younger cohort (0.23%). The authors attributed this high mortality rate to the negative influence of hyperthermic intraperitoneal chemotherapy on the renal function of their elderly cohort (i.e., increased serum creatinine levels), and suggested that the systemic toxicity promoted by hyperthermic intraperitoneal che-



motherapy resulted in renal insufficiency and, ultimately, led to higher mortality outcomes in their elderly cohort. On the other hand, Beckert et al<sup>23</sup>, and Spiliotis et al<sup>26</sup> reported no differences in the events of mortality between their younger and their elder cohort. However, this lack of difference may be explained by the smaller sample size of the older cohort as compared to the younger cohort in these studies. For instance, in the case of Beckert et al<sup>23</sup> while 352 patients were evaluated in the younger cohort only 29 patients were included in the elderly cohort. Similarly, for Spiliotis et al<sup>26</sup>, 70 patients were evaluated in the younger cohort while only 30 patients were evaluated in the elderly cohort. Our meta-analysis reports higher risks of postoperative mortality (OR: 3.28) in elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as compared to the younger patients. Subsequent subgroup analyses further confirmed that the risks of postoperative mortality were high for elderly patients in both types of studies reporting the cut-off age at 65 (OR: 4.16), and 70 years (OR 1.94).

Despite being a novel study, this systematic review and meta-analysis has several limitations. First and foremost, this study was not pre-registered in a systematic review repository such as PROSPERO York or Joanna Briggs Institute, which may raise concerns about the validity of this current review<sup>41</sup>. Several attempts were made by us to register this present review, but due to the current COVID-19 pandemic crisis, registration times at the repositories have been extended by more than one year. Secondly, we observed that the included studies in our review had segregated the young and elderly population groups at different cut-off ages. While 9 studies had reported the age cut-off at 65 years<sup>11,12,15,16,18-21,25</sup>, only 4 studies had reported the cut-off at 70 years<sup>22-24,26</sup>. In our analyses of postoperative complications, there was a moderate heterogeneity detected in one of the subgroup analyses i.e., 70-year cut-off age. Therefore, we recommend our readers interpret these findings carefully as we cannot rule out the possibility of incurring bias. Further studies to address these limitations (i.e., by reporting similar cut-off ages) would allow clinicians to better interpret the morbidity and mortality-related risks imposed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on elderly population groups.

## Conclusions

We provide updated evidence of poor morbidity and mortality outcomes in elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as compared to their younger counterparts. The study also provides novel evidence of no difference in the incidences of anastomotic leakage and overall duration of hospital stay between younger and elderly patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Taking into account the existing literature<sup>42</sup>, we recommend the development of multidisciplinary task forces that include specialized nursing professionals and oncologic surgeons to develop best practice guidelines for improving prognostic outcomes for patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request..

## Authors' Contribution

JT conceived and designed the study. PJ and JS collected the data and performed the literature search. JT was involved in the writing of the manuscript. YL edited the manuscript. All authors have read and approved the final manuscript.

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