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Title

Pre-operative prognostic factors for 5-year survival following pulmonary metastasectomy from colorectal cancer. A systematic review and meta-analysis.

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Visual Abstract

Key question: Which pre-operative factors affect 5-year survival post-pulmonary metastasectomy?

Key findings: We identified 11 factors with favorable and statistically significant prognostic effects on 5-year survival post-PM.

Take-home message: Solitary unilateral metastasis <2cm in size were among the favorable pre-operative prognostic factors while disease free interval at 24months was not.

Abstract

Objectives

We seek to identify pre-operative prognostic factors and measure their effect on 5-year survival following Pulmonary Metastasectomy (PM) for Colorectal Cancer (CRC).

Methods

We systematically reviewed the databases of Cochrane Library, MEDLINE, Embase and Google Scholar from January 2000-April 2021 to identify pre-operative factors that have been investigated for their prognostic effect on survival following PM. Quality assessment was performed using the QUIPS tool. The prognostic effect of each identified factor on 5-year survival post PM was estimated using random-effects meta-analyses.

Results

We identified 115 eligible articles which included 13,294 patients who underwent PM from CRC. The overall 5-year survival after resection of the lung metastasis was 54.1%. The risk of bias of the included studies was at least moderate in 93% (107/115). Seventy-seven pre-operative factors had been investigated for their prognostic effect. Our analysis showed that 11 factors had favorable and statistically significant prognostic effect on 5-year survival post-PM. These included solitary metastasis, size <2cm, unilateral location, N0 thoracic disease, no history of extra-thoracic or liver metastasis, normal carcinoembryonic antigen levels both before PM and CRC excision, no neo-adjuvant chemotherapy before PM, CRC T-stage < T4 and

no p53 mutations on CRC. Disease free interval at 24months did not appear to affect 5-year survival.

Conclusion

Despite the considerable risk of bias in the literature, our study consolidates the available evidence on pre-operative prognostic factors for PM from CRC. These findings can complement both clinical practice and the design of future research on the field of PM.

Keywords: Pulmonary metastasectomy, Colorectal cancer, Prognostic factors, 5-year Survival, Meta-analysis

Main Text

Abbreviations and acronyms

ASA: American Society of Anesthesiologists

BMI: Body Mass Index

CA 19-9: Carbohydrate antigen 19-9

CCI: Charlson Comorbidity Index

CEA: Carcinoembryonic Antigen

CRC: Colorectal Cancer

CRP: C-Reactive Protein

DFI: Disease Free Interval

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

GECMP-CCR: Spanish Group of Lung Metastases of Colo-Rectal Cancer

HR: Hazard Ratio

IQR: Interquartile Range

KRAS gene: Kirsten Rat Sarcoma virus gene

MESH: Medical Subject Heading

Nd:YAG laser: Neodymium-doped Yttrium Aluminum Garnet laser

NLR: Neutrophil/Lymphocyte Ratio

PET: Positron Emission Tomography

PM: Pulmonary Metastasectomy

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROGRESS: PROGnosis RESearch Strategy

PulMiCC study : Pulmonary Metastasectomy in Colorectal Cancer study

QUIPS: Quality In Prognosis Studies

RATS: Robotic-Assisted Thoracoscopic Surgery

REML: restricted maximum likelihood

SABR: Stereotactic ablative radiotherapy

VATS: Video-Assisted Thoracoscopic Surgery

Introduction

Pulmonary metastasectomy (PM) is a widely performed procedure offered to patients with lung metastases and has been described as a “pillar of modern thoracic surgery [1,2]. The accepted criteria for patients to be eligible for this procedure include the following: (1) complete resection (R0) must be technically feasible, (2) the patient must be able to tolerate pulmonary resection, (3) control of the primary tumor must be warranted and (4) no extra-thoracic lesion must be detectable [3].

A landmark cohort study which encouraged this practice was published in 1997 and included 5206 patients from Europe and North America [4]. Following that study, systematic reviews and meta-analyses of single- and multi-institutional reports have attempted to estimate the survival benefit following the procedure. However, as the existing literature is largely comprised of retrospective studies, which lack a control group, the actual benefit of pulmonary metastasectomy on survival remains uncertain [5-9]. Unfortunately, a citation cascade in the literature of these low-evidence studies, has created a belief system, which means that this uncertainty is often disregarded [10]. Furthermore, multiple case-series that reported the percentage of patients who proceeded with PM indicate that this procedure is performed in a small proportion of these patients (1%-6.5%) [11-13]. This demonstrates that these studies are comprised of a highly selective patient population and therefore could represent a group of patients with inherently favorable prognosis. However, despite that this ambiguity is even acknowledged in a recent expert consensus [3], the number of PM appears to be increasing [14,15].

Launched in 2010, the PulMiCC trial was the first and to-date only randomized clinical trial in the field that investigated the evidence for PM of colorectal metastases [16]. The trial was closed prematurely in 2016 due to poor recruitment [16]. The trial investigators identified that clinicians remained reluctant to enroll patients to a study that did not offer the procedure to half of its participants.

Following reflection on the outcome of PulMiCC trial, there is a clear need to improve recruitment for future randomised trials. A well-developed prognostic

model for 5-year survival following pulmonary metastasectomy based on pre-operative factors could enhance recruitment by stratifying patients to different risk groups, thus increasing the clinical equipoise of a future trial. To develop such a model, the first stage requires an updated and broad systematic review and meta-analysis of prognostic factors to identify which pre-operative characteristics affect 5-year survival following pulmonary metastasectomy, stratified by primary cancer site. Following this, based on using individual participant data, the prognostic model can be constructed.

In the present paper, we report on the first stage of this process, the results of our broad search and a systematic review and meta-analysis for the most frequently published primary site of origin which was colorectal cancer (CRC).

Methods

A protocol for this study was designed and is available on PROSPERO (CRD42021247133). This study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Checklist is provided in the Appendix) [17] and this study followed the PROGRESS (PROGnosis RESearch Strategy) framework, which classifies this review as prognostic factor research (type 2) [18, 19]. Note that as our primary goal was to identify the

prognostic factors associated with 5-year survival following pulmonary metastasectomy, indicator and comparative factors were not applicable.

Eligibility criteria

Studies were eligible if they: (1) included adults undergoing complete resection of pulmonary metastases with either open, thoracoscopic or robotic surgery, (2) contained at least 40 patients, (3) reported at least one pre-operative prognostic factor, (4) reported follow-up of at least five years for overall survival, (5) did not include patients treated with non-invasive approaches, patients undergoing repeat pulmonary resection, and patients with a history of metastases in other organs.

Articles published in a language other than English and those with a full text unavailable were recorded but excluded. Further, we restricted our studies to be published since January 2000 to reflect modern anaesthetic methods, surgical techniques, and perioperative management. For studies with overlapping patient cohorts, we only included the most recently published article to avoid duplication of data.

Search strategy

To achieve a broad and inclusive review of the literature we used only keywords relevant to the disease of lung metastasis and the operation of PM. For that reason, our search strategy was designed without focus on a particular primary cancer site. We searched the Cochrane Library, MEDLINE, Embase and Google Scholar for

relevant articles. The search strategy included key words such as “pulmonary metastases”, “metastasectomy”, “pneumonectomy”, “thoracotomy” and “thoracic surgery” with limitation only on human trials, English language and publication from the January 2000 until April 2021 as aforementioned.

The detailed search strategy can be found in the Appendix B.

Selection of studies

A two-stage screening process was adopted. Initially, records were screened by title and abstract, with reference lists of potentially eligible articles hand-searched to further identify records. In the second stage, full texts of all potentially eligible articles were reviewed to confirm eligibility. In both stages, two reviewers (AG, CK) independently screened records in duplicate, with disagreements resolved through discussion. If a consensus could not be reached, then the other members of the team were consulted.

Data extraction and study quality assessment

Data extraction forms were designed, reviewed and approved by the entire review team following the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prognostic factor studies (example form in Appendix B) [19]. In brief, these forms collected general information about each study, demographics and baseline characteristics of study participants, procedural characteristics, outcome information and details to undertake the quality assessment. Data were double

extracted independently by two reviewers (AG, CK), with disagreements again resolved through discussion and further consultation with the team if required.

Eligible studies were assessed using the quality in prognostic factor studies (QUIPS) tool [18,19]. Each of the six domains from the QUIPS tool were assessed and these scores were used to assign each study an overall risk of bias score (Low/Moderate/High). These assessments were completed in duplicate and independently by two reviewers (AG, CK). Any disagreements on the overall score between the two reviewers were resolved through discussion with the rest of the team.

Statistical analysis

Categorical variables were expressed as proportions and percentages. Continuous variables were summarised with mean and standard deviation or median and interquartile range. For studies that did not report 5-year survival rates, these values were estimated directly from Kaplan–Meier curves using WebPlotDigitizer (https://apps.automeris.io/wpd/).

Meta-analyses were performed for each prognostic factor where unadjusted hazard ratios (HR) of the prognostic effect on 5-year overall survival were available for at least two studies. If HR and corresponding confidence interval for the prognostic effect of a factor on 5-year survival was not reported, we used the approach of Parmar et al. [20], when appropriate, to obtain our own estimates of prognostic factor effect and uncertainty on 5-year survival. For continuous factors that were

categorised, we chose the cut-point that provided the largest amount of data. The overall number of studies and patients that investigated each factor was calculated without duplicate calculations when different cut points were evaluated in the same sample.

Our primary approach to data synthesis was to use a random-effects model with the restricted maximum likelihood (REML) estimator with Hartung-Knapp-Sidik-Jonkman correction [20]. However, if the number of included studies was less than three, then the REML estimator was used without correction [21]. Heterogeneity for the effect of each pre-operative prognostic factor was assessed using the Cochrane's Q-test and inconsistency between studies was estimated using the I^2 statistic. Statistical significance was assumed for p-values≤0.05.

Analyses were performed using STATA 17 (StataCorp. 2019. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Results

Systematic Review

Our search identified 4479 records, and after the first stage of screening we identified 508 potentially eligible studies across all primary cancers (Figure 1).

Colorectal cancer was the most frequently reported primary site, accounting for 38% of studies (194/508), and in the present paper we focus on CRC.

After full-text review of the CRC papers, 115 studies were included in our systematic review, comprising of 13,294 patients who underwent PM from CRC (full reference list can be found in Appendix A). The overall 5-year survival was reported in 96 studies with a range from 24% to 72% (Table A, Appendix A). Regression analysis revealed strong correlation between the year of publication and the reported 5-year survival following PM ($p<0.001$). This demonstrated a clear trend in improved post-operative survival throughout the investigated period of our review. All the included studies were observational and 81% (93/115) reported data from a single institution. The majority of studies (92%, 106/115) had at least moderate risk of bias according to QUIPS tool (Table 1).

Thoracotomy was the predominant surgical approach for PM in 74% (55/74) amongst studies. There was a clear trend of increasing use of Video-Assisted Thoracoscopic Surgery (VATS) for PM in studies published after 2010 compared to the first decade of the century ($p<0.001$). However, thoracotomy remained the most favorable approach even among studies that were published after 2010. The most frequent lung excision for PM was wedge resection which was preferred in 82% (78/95) of the studies. Wedge resection was followed by lobectomy and segmentectomy as the next most common lung excision while pneumonectomy was less frequently performed (Table 1).

We identified 77 pre-operative factors that were investigated for their influence on survival post PM. Seventeen of these factors were chosen for their clinical and statistical significance and shown in Table 2 whereas a full detail of all 77 factors can be found in Table B of the Appendix. We also found two factors that assessed the interval between lung metastasis and CRC. The metastatic disease was defined as synchronous or metachronous based on whether it was diagnosed within the first 6 months or later from CRC diagnosis while DFI was described as the time interval between CRC resection and the diagnosis of lung metastasis.

The most frequently investigated pre-operative factor was the number of metastases (62%, 71/115). This was followed by gender and DFI, both were assessed in 57% (65/115) of the studies. Age was the third most common factor and was reviewed for its prognostic effect on survival by 53% (61/115) of the publications (Table 2). Thirty-two specific genes from the primary cancer have also been investigated but only KRAS and p53 were assessed by more than one study. Apart from the CRC genes, we identified 21 more factors that were reported in less than 5 studies with 12 of them being assessed in single studies (Table B, Appendix).

The only factors that demonstrated a median p-value<0.05 were the number of pulmonary metastases, pre-PM Neutrophil/Lymphocyte Ratio and pre-PM C-Reactive Protein (CRP). However, the latter two factors were each investigated in only 3 studies respectively, which included 665 and 340 patients respectively.

We found great inconsistency and variability in the cut points that were used for 9 of the reported factors. Most notably, age was dichotomized in 12 different values followed by DFI and CRC stage which were explored by 7 different thresholds. Also, we discovered that some studies explored multiple thresholds for the same factor. The total number of patients and studies that investigated each pre-operative factor at a certain value is presented in Table B of the Appendix.

Meta-analysis

For our quantitative synthesis, 77 studies provided adequate data in their reports in order to estimate the effect of at least one pre-operative factor on 5-year survival. The total number of patients included in at least one meta-analysis were 9935. The overall 5-year survival from these studies was estimated at 54.1%.

In total, 41 pre-operative factors were evaluated for their prognostic effect on 5-year post-operative survival. The factors that were assessed by at least two studies and could therefore be included in a meta-analysis were 24. We demonstrate the results from the pooled estimated prognostic effect of 21 clinically important pre-operative factors in Table 3. A detailed report of all 41 identified factors is shown in Table C of the Appendix.

Age was explored in 22 studies which included 3924 patients. More than half of these studies (55%, 12/22) used cut points ranging from 65 to 70 years (</>65 years: 4 studies, </>67 years: 1 study and </>70 years: 7 studies). These studies comprised

75% (2951/3924) of the patients who offered data for the prognostic effect of age compared to merely 57% (2225/3924) from the 7 studies that used only the 70 year-threshold. Therefore, we decided to include all 12 studies in our meta-analysis for age as this would utilize most of the available evidence for that factor with an acceptable risk of bias from addressing patients who were 65 years old as if they were 70. Age >70 had HR: 1.00 (95%CI: 0.88-1.13) for 5-year post-operative survival. There was no evidence of heterogeneity among the studies (I^2: 0%, Cochrane's Q-test: 0.537).

From our meta-analysis, the factors that demonstrated favorable 5-year prognosis were the following: unilateral site of metastasis {HR (95%CI): 1.59 (1.34 – 1.89); I^2=23%}(Figure 1, Appendix); normal CEA level before PM {HR (95%CI): 1.77 (1.55 – 2.01); I^2=42.6%}(Figure 2, Appendix) and before primary tumor excision{HR (95%CI): 1.38 (1.01 – 1.90); I^2=0%}; single lung metastasis {HR (95%CI): 1.67 (1.52 – 1.82); I^2=0%} (Figure 3, Appendix); size of metastasis <2cm {HR (95%CI): 1.37 (1.15 – 1.64); I^2=43.1%}; absence of metastatic disease in thoracic lymph nodes {HR (95%CI): 2.05 (1.79– 2.35); I^2=11.4%}(Figure 4, Appendix); no administration of neo-adjuvant chemotherapy before PM {HR (95%CI): 1.72 (1.18 – 2.52); I^2=46.3%}; no past medical history of extra-thoracic {HR (95%CI): 1.33 (1.15 – 1.55); I^2=46.6%}(Figure 5, Appendix) or liver metastasis {HR (95%CI): 1.30 (1.12 – 1.50); I^2=30.6%}. The only primary tumor characteristics that appeared significant prognostic factors were CRC T-stage < T4{HR (95%CI): 1.77 (1.20– 2.62); I^2=0%} and no mutation of p53 in primary cancer {HR (95%CI): 1.81 (1.04 – 3.16); I^2=0%} (Table 3).

The data for thoracic lymph node status arguably is not derived purely from pre-operative information as some papers either did not clarify if thoracic lymph node status was assessed only based on pathology reports or they combine pathological with clinical/radiological findings. Therefore, given that this information could be available from pre-operative scans we decided to include all the available evidence in our analysis.

Another interesting finding was that the time interval between the diagnosis of lung metastasis and primary cancer did not appear to influence prognosis. In particular, neither DFI < or > 24months nor synchronous or metachronous diagnosis of lung metastasis showed a significant effect on post-operative survival, HR (95%CI): 1.06 (0.83 – 1.35); I^2=51.9% (Figure 2) and HR (95%CI): 1.19 (0.95 – 1.48); I^2=0% respectively (Figure 3).

Finally, 17 prognostic factors were evaluated for their effect on 5-year post-PM survival only once in the literature. From these factors, 6 showed statistically significant prognostic effect in univariable analysis. Those included, tumor response to neo-adjuvant chemotherapy {HR (95%CI): 5.41 (1.98 – 14.78)}; American Society of Anesthesiologists (ASA) physical status classification system {HR (95%CI): 1.66 (1.08 – 2.56)}; Neutrophil-to-Lymphocyte Ratio (NLR) {HR (95%CI): 1.61 (1.27 – 2.06)}; difference between the maximum and minimum tumor diameters {HR (95%CI): 1.57 (1.06 – 2.34)}; tumor doubling time {HR (95%CI): 4.17 (1.84-9.42)} and BRAF mutation status on primary tumor {HR (95%CI): 13.84 (3.72 – 51.57)} (Figure 3).

Discussion

To our knowledge, this is the first project that attempts to consolidate all the available evidence on pre-operative prognostic factors for PM from CRC. Our systematic review of the literature showed great variety of pre-operative factors that have been investigated for their prognostic effect on survival post PM. In total, we identified 77 factors that had been explored at least in one study. Furthermore, our findings highlight the great heterogeneity on reporting and analysis of prognostic factors for PM. This results from the inconsistency amongst the various cut points that have been used to explore these factors by different researchers. Also, our study includes the first meta-analysis on prognostic effect of pre-operative factors on 5-year survival after PM. This has not been explored previously, as previous studies have focused on the effect of prognostic factors on overall survival [5,22-24]. In our meta-analysis, we identified 11 pre-operative factors that appear to effect 5-year survival. From the factors that were investigated only by one study, we found 6 additional factors that demonstrated significant prognostic effect.

The four characteristics of metastatic tumors that showed evidence of worse 5-year survival in our meta-analysis were bilateral location, >1 lung metastasis, size > 2cm and presence of metastatic disease in thoracic lymph nodes. These findings agree with previous meta-analyses in PM from CRC metastases, that have explored the same factors for their prognostic value on overall survival [5,22-24]. However, three of the previously published meta-analysis [5,22,23] had smaller sample size and number of included studies which is justified due to shorter investigated period

compared to our study. The third study is the only one that reported larger sample size from ours despite including smaller number of studies for these 4 factors [24]. This is attributed to the use of overlapping cohorts in that study. The investigators used data from the same pool of patients in their meta-analysis multiple times. Therefore, we argue that our study is not only more inclusive but also uses more appropriate methodology compared to previously published material in the field of prognostic research for PM from CRC.

We identified three clinical findings related to the metastatic disease that had a statistically significant effect on our outcome of interest. These included the administration of neo-adjuvant chemotherapy before PM and the history of extra-thoracic and liver metastasis. This result contradicts the findings of a recent meta-analysis on peri-operative chemotherapy [25] which showed favorable overall survival {HR (95% CI): 0.83 (0.75-0.92)}. However, that analysis involved data from mostly adjuvant chemotherapy which we did not consider as a pre-operative factor and therefore did not include in our models. Despite that our data derive from contemporary publications, as all 8 contributing studies were published after 2010, this result needs careful interpretation because we did not perform our analysis based on particular chemotherapy regimens.

Even though history of liver metastasis before PM was not associated with post-PM survival in a meta-analysis of aggregate data from 2013 [22], a more recent individual data meta-analysis from 2018 [5] showed that a history of liver metastases

was a negative prognostic factor for survival. Our results validate the findings from the individual data meta-analysis providing a larger sample size from more studies.

Furthermore, we demonstrated significant prognostic effect of four factors, which were related to the primary tumor. These were CRC T-stage, p53 mutation status and CEA levels both before laparotomy and PM. Elevated CEA levels before PM have shown a negative prognostic effect in all previously published meta-analyses [5,22-24]. Even though, the remaining three primary tumor characteristics included data from merely 2 studies, there was no evidence of inconsistency between them (Table 3). From these 3 factors, only CRC T-stage has been previously associated with an impact on post-operative survival in a meta-analysis [24].

An interesting finding from our study, was that the time interval between the incidence of CRC and lung metastasis did not appear to affect 5-year survival following PM. A diagnosis of lung metastasis close to the primary cancer has been considered an indicator of tumor aggression and wider disease spread [22]. Therefore, short DFI and synchronous metastatic disease has been associated with worse prognosis for survival [26]. However, our findings contradict that argument and differ from the results of previous meta-analyses [22-24]. To interpret this, we reviewed the data from these studies in detail. The first meta-analysis by Gonzalez et al. [22] did not use a specific cut point for DFI. Instead, they included all the available data on DFI in their forest plot regardless of what cut point was used in the original studies. That approach assumes that patients who have DFI above 12 months [27,28] share the same hazard of overall survival with those who have DFI above 36months

[29,30]. However, that assumption contradicts with their conclusion that shorter DFI represents more aggressive and therefore more deadly disease. Furthermore, they included a paper in their analysis [31] that investigated the prognostic effect of DFI on Recurrence Free Survival and not Overall Survival. Similar issues were identified in the paper by Huang et al. [24]. Even though they present that DFI ≤2 years had HR (95%CI): 1.705 (1.518−1.915); I^2=0%, their analysis included 4 studies which investigated DFI at 12 months [32-35], 2 studies at 36 months [36,37] and 1 at 6months [38]. Furthermore, 2 studies that reflect 23.28% of the weight in their meta-analysis derive their sample from the same pool of patients from 46 Japanese institutions [39,40] which inadvertently introduces bias in the results.

The only study that reviewed DFI at a specific cut point (36months) and also included individual patient data was the study by Salah et al [23]. Their analysis resulted in favorable prognostic outcome on 5-year post-operative survival for patients with DFI ≥ 36months {HR (95%CI): 0.81 (0.66-0.99)}. Even though, this finding contradicts the results of our analysis, it is important to highlight that our sample size was almost double of that by Salah et al [23]. Also, our study includes the complementary result that diagnosis of synchronous or metachronous lung metastasis does not appear to affect 5-year survival post PM {HR (95%CI): 1.19 (0.95 – 1.48); I^2=0%}. Therefore, we believe that current evidence suggests that the time of diagnosis for lung metastases from CRC does not offer a prognostic effect on 5-year post-operative survival. Nonetheless, we acknowledge that the available evidence has significant limitations as it derives from retrospectively collected data from multiple centers that adhere to

different follow-up protocols which inadvertently impact the time of diagnosis in metastatic disease.

Furthermore, our analysis showed that there was a statistically significant improvement in 5-year survival post PM during the investigated period ($p<0.001$). This can be attributed to many factors that lead to better quality of care and improved overall survival after thoracic surgery. Those include new chemotherapy or molecular-targeted agents, the adaption of enhanced recovery protocols and new operating and anaesthetic techniques. This result also justifies our rationale to exclude studies that were published before the year 2000 as we wanted our analysis to reflect more contemporary practice.

There are several limitations in our study. First, the majority of the included studies (93%, 107/115) were assessed with at least moderate risk-of-bias according to the QUIPS tool. Lack of uniformity in reporting among the eligible studies resulted in only 67% (77/115) of them contributing data to our study. Therefore, despite the large number of included patients in our analysis, 25% (3359/13294) of eligible patients could not be included. Furthermore, since the majority of our data is derived from single center, observational studies, there was great inconsistency on treatment and follow-up protocols among the different institutions. This inevitably introduces bias on several analysed factors like DFI and chemotherapy administration. For systematic therapies in particular, some studies either did not report the administered regimens [41,42] or they even used variable regimens over the course of their investigated period [43,44]. In either case, when they reviewed

the administration of chemotherapy as prognostic factor for 5-year survival in their cohort, most of them did not perform separate analysis according to specific regimens but instead they assessed chemotherapy administration as a single, all-inclusive factor [41-44]. Therefore, this made it impossible for us to conduct meta-analysis on different systemic therapies for their prognostic effect. However, studies that examined specific agents before PM, such as Bevacizumab, for their influence on 5-year survival were reported accordingly [45]. Finally, our search strategy included studies until April 2021 and we only used Medical Subject Heading (MESH) terms when searching for PM, and did not additionally include keywords in this part of the search. We acknowledge that this approach may not have identified all of the most current literature. Nonetheless, our results currently provide the best available and more up-to-date evidence on pre-operative prognostic factors for 5-year survival following PM.

In light of new upcoming techniques like SABR on the field of treating pulmonary metastases [46], we need to better understand the significance and benefit of PM on survival. The PULMICC trial unfortunately failed to recruit enough patients mainly because of clinician hesitancy towards active monitoring and their preference to proceed with the operation [16]. Our study consolidates the knowledge on investigated pre-operative factors and therefore provides valuable information for the design of future prospective research in the field of PM from CRC. This helps to establish a common ground for discussion in order to reach a wider consensus on inclusion criteria for future research.

Conclusion

We reviewed the existing literature for pre-operative factors that affect prognosis for 5-year survival following pulmonary metastasectomy. We consider the most clinically significant factors to be solitary lung metastasis, <2cm in size, normal CEA levels before PM, absence of thoracic lymph node disease and no history of extra thoracic or liver metastases. This study presents the best available evidence on prognostic research in the field of PM from CRC. Our results can act as a stepping stone towards achieving better recruitment on clinical trials that investigate pulmonary metastasectomy and provide the best current level of evidence to complement clinical decision making.

Table 1.	
Characteristic	**Total (%)**
Patients	13,294
Study Design	
Multi-centre	22 (19%)
Single Centre	93 (81%)
Retrospective	114 (99%)
Prospective	1 (1%)

Surgical Approach	
Total	19518
Open	7,554 (39%)
Unilateral Thoracotomy	6,813 (90%)
Bilteral Thoracotomies	34 (0.5%)
Clamshell Thoracotomy	7 (0.09%)
Sternotomy	223 (3%)
N/S	477 (6%)

Minimally Invasive		3,268 (17%)
VATS		3,115 (95%)
RATS		11 (0.3%)
Transdiaphragmatic		24 (0.7%)
N/S (VATS or RATS)		118 (4%)
N/R		8,696 (44%)
Lung Parenchyma excision		
Total		20,916

Sublobar		12,107 (60%)
Wedge		8,432 (70%)
Segmentectomy		1,286 (11%)
Combination		765 (6%)
Wedge+Segmentectomy		
N/S		1,624 (13%)

Lobectomy and Above		4,088 (20%)
Lobectomy		3,282 (80%)
Combination (Lobectomy + Wedge/Segmentectomy, Bilobectomy)		243 (6%)
Pneumonectomy		211 (5%)
N/S		352 (7%)
N/S		4,001 (20%)
5-Year Survival		Median: 50% IQR: 42-58.4%

QUIPS score	
High	41 (36%)
Moderate	65 (56%)
Low	9 (8%)

Baseline characteristics and risk of bias assessment of 115 identified eligible studies.IQR: Interquartile Range; N/S: Not Specified; QUIPS: Quality In Prognosis Studies; RATS: Robotic-Assisted Thoracoscopic Surgery; VATS: Video-Assisted Thoracoscopic Surgery.

Prognostic Factor	Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
Cut point				

		10254	61		
		• 71	• 1		
	• 45 years	• 442	• 4		
	• 50 years	• 1183	• 10		
	• 60 years	• 100	• 1		
	• 61 years	• 49	• 1		
	• 62 years	• 156	• 2	5/61	0.478
Age	• 62.7 years	• 247	• 2	(8.2%)	(0.088-0.680)
	• 63 years	• 57	• 1		
	• 64 years	• 1800	• 10		
	• 65 years	• 49	• 1		
	• 66 years	• 131	• 1		
	• 67 years	• 3136	• 11		
	• 70 years	• 2869	• 20		

Prognostic Factor	Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
Cut point				
• N/R or Continuous				

Prognostic Factor		Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
Cut point					
Gender	Male/Female	10329	65	6/65 (9.2%)	0.440 (0.131-0.859)
Number of Metastases		11545	71	41/71 (57.7%)	0.040 (0.007-0.220)
	• 1	• 9677	• 61		
	• 2	• 1987	• 8		
	• 3	• 570	• 3		
	• 4	• 56	• 1		
	• 5	• 140	• 2		
	• N/R	• 148	• 2		

Prognostic Factor		Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
Cut point					
Size of larger Metastases		9122	56	13/56 (23.2%)	0.288 (0.053-0.606)
	• 1cm	• 736	• 2		
	• 1.5cm	• 394	• 2		
	• 2cm	• 4197	• 23		
	• 3cm	• 2024	• 21		
	• 5cm	• 210	• 2		
	• N/R or Continuous	• 1974	• 10		

		6509	65		
DFI (months)	• 6mo • 12mo • 18mo • 20mo • 24mo • 30mo • 36mo • Continuous • N/R	• 96 • 3184 • 73 • 306 • 3462 • 626 • 1971 • 614 • 1293	• 1 • 19 • 2 • 1 • 28 • 1 • 17 • 5 • 6	20/65 (30.8%)	0.250 (0.040-0.530)
Site of Metastasis	Unilateral / Bilateral	6402	42	16/42 (38%)	0.177 (0.022-0.445)
Pre-PM CEA	Elevated / Normal	7397	59	30/59 (50.8%)	0.057 (0.018-0.254)

Prognostic Factor		Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
Cut point					
Pre CRC Resection CEA	Elevated / Normal	687	6	2/6 (33.3%)	0.091 (0.04-0.200)
Thoracic Lymph Node Status	N0 / N+	6036	41	24/41 (58.5%)	0.05 (0.020-0.170)
Pre-PM Neoadjuvant Chemotherapy	Yes / No	3421	22	7/22 (31.8%)	0.268 (0.032-0.700)
Time of Metastasis Diagnosis	Synchronous / Metachronous	3299	25	3/25 (12%)	0.454 (0.184-0.585)

Prognostic Factor	Cut point	Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
History of Extra-thoracic Metastasis	Yes / No	8863	53	13/53 (24.5%)	0.399 (0.069 – 0.616)
History of Liver Metastasis	Yes / No	7803	46	9/46 (19.6%)	0.389 (0.089-0.558)

CRC Stage	<u>TNM:</u> • I, II / III, IV • I, II, III / IV • I / IV • I / II, III • II / III • <u>Duke's:</u> • A, B / >B • A / >A • N/R	4343 • 1439 • 373 • 194 • 59 • 153 • 327 • 118 • 1680	36 • 11 • 3 • 1 • 1 • 2 • 4 • 1 • 14	6/36 (16.7%)	0.280 (0.098-0.673)
CRC T Stage	• T3 • T4	3098 • 905 • 481	18 • 7 • 3	4/18 (22.2%)	0.279 (0.098-0.420)

Prognostic Factor		Number of patients included in the studies	Studies Investigating the factor	Studies that demonstrated significance at 5% (%)	Median p-value (IQR)
Cut point					
	• N/R	• 1712	• 8		
Pre-PM CRP	Elevated / Normal	340	3	2/3 (66.6%)	0.034 (0.003-0.620)
NLR	Elevated / Normal	665	3	2/3 (66.6%)	0.047 (<0.0001- 0.120)

Table 2 Pre-operative factors assessed for their prognostic effect on post-pulmonary metastasectomy survival. CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; CRP: C-Reactive Protein; DFI: Disease Free Interval; NLR: Neutrophil-to-Lymphocyte Ratio; N/R: Not Reported.

Factor	Studies	Patients Total	Patients Control	Patients Research	HR (95%CI)	Heterogeneity	
						I^2	Cochrane's Q-test
META-ANALYSIS							
Age	12	2951	**<70** 1986	**>70** 965	1.00 (0.88 - 1.13)	0%	0.537
Gender	28	4966	**Female:** 1971	**Male:** 2995	1.03 (0.89 – 1.19)	51.9%	0.001
Site of Metastases	22	3117	**Unilateral:** 2513	**Bilateral:** 604	1.59 (1.34 – 1.89)	23%	0.162
Pre-PM CEA	32	4255	**Normal:** 2390	**Elevated:** 1865	1.77 (1.55 – 2.01)	42.6%	0.006

Factor	Studies	Patients Total	Patients Control	Patients Research	HR (95%CI)	Heterogeneity	
						I^2	Cochrane's Q-test
Pre-Laparotomy CEA	2	355	**Normal**: 165	**Elevated**: 165	1.38 (1.01 – 1.90) *	0%	1.000
Number of Metastases	32	4730	**Solitary:** 2904	**Multiple**: 1826	1.66 (1.52 – 1.82)	1.6%	0.441
Size of Metastasis	14	2974	**<2cm:** 1463	**>2cm:** 1511	1.37 (1.15 – 1.64)	43.1%	0.043
Thoracic Lymph Node Status	27	3978	**No:** 3335	**N+:** 643	2.05 (1.79– 2.35)	11.4%	0.294

Factor	Studies	Patients Total	Patients Control	Patients Research	HR (95%CI)	Heterogeneity	
						I^2	Cochrane's Q-test
Neo-adjuvant Chemotherapy before PM	8	1550	**No:** 1214	**Yes:** 336	1.72 (1.18 – 2.52)	46.3%	0.071
DFI	13	1787	**<24mo:** 875	**>24mo:** 914	1.06 (0.83 – 1.35)	51.9%	0.015
Lung Metastasis Diagnosis	10	1527	**Metachronous:** 1247	**Synchronous:** 280	1.19 (0.95 – 1.48)	0%	0.518
History of Extra-thoracic Metastases	27	5007	**No:** 3671	**Yes:** 1336	1.33 (1.15 - 1.55)	46.6%	0.005

Factor	Studies	Patients Total	Patients Control	Patients Research	HR (95%CI)	Heterogeneity	
						I^2	Cochrane's Q-test
History of Liver Metastasis	21	3956	**No:** 2977	**Yes:** 979	1.30 (1.12 – 1.50)	30.6%	0.091
CRC T Stage	2	422	**<T4:** 336	**T4:** 86	1.77 (1.20– 2.62) *	0%	0.492
CRC p53 Mutations	2	218	**Negative:** 93	**Positive:** 125	1.81 (1.04 – 3.16) *	0%	0.775
Factors investigated by a single study							

Factor	Studies	Patients Total	Patients Control	Patients Research	HR (95%CI)	Heterogeneity	
						I^2	Cochrane's Q-test
Tumor response to Neo-adjuvant Chemotherapy before PM	1	58	**Yes:** 50	**No:** 8	5.41 (1.98 – 14.78)	N/A	N/A
Performance Status before PM	1	354	**ASA = 1:** 282	**ASA >1:** 72	1.66 (1.08 – 2.56)	N/A	N/A
NLR	1	574	**< 4.05:** 239	**> 4.05:** 335	1.61 (1.27 – 2.06)	N/A	N/A
Dmax- Dmin	1	247	**≤2cm:** 167	**>2cm:** 80	1.57 (1.06 – 2.34)	N/A	N/A

Factor	Studies	Patients Total	Patients Control	Patients Research	HR (95%CI)	Heterogeneity	
						I^2	Cochrane's Q-test
Tumor Doubling Time	1	65	**>100 Days:** 34	**< 100 Days:** 31	4.17 (1.84 – 9.42)	N/A	N/A
BRAF status in primary tumor	1	87	**Wild-Type:** 68	**Mutant:** 19	13.84 (3.72 – 51.57)	N/A	N/A

Table 3. Prognostic effect of pre-operative factors on 5-year survival following PM. ASA: American Society of Anesthesiologists physical status classification system; CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; DFI: Disease Free Interval; Dmax: Maximum Diameter; Dmin: Minimum Diameter; NLR: Neutrophil-to-Lymphocyte Ratio; PM: Pulmonary Metastasectomy; WT: Wild-type.

*Pooled estimate was calculated random effects model with restricted maximum likelihood (REML) estimator without Hartung-Knapp-Sidik-Jonkman correction.

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Data Availability Statement

The data underlying this article that are publicly available are included in either the Main text or the Appendix.

Figure Legends

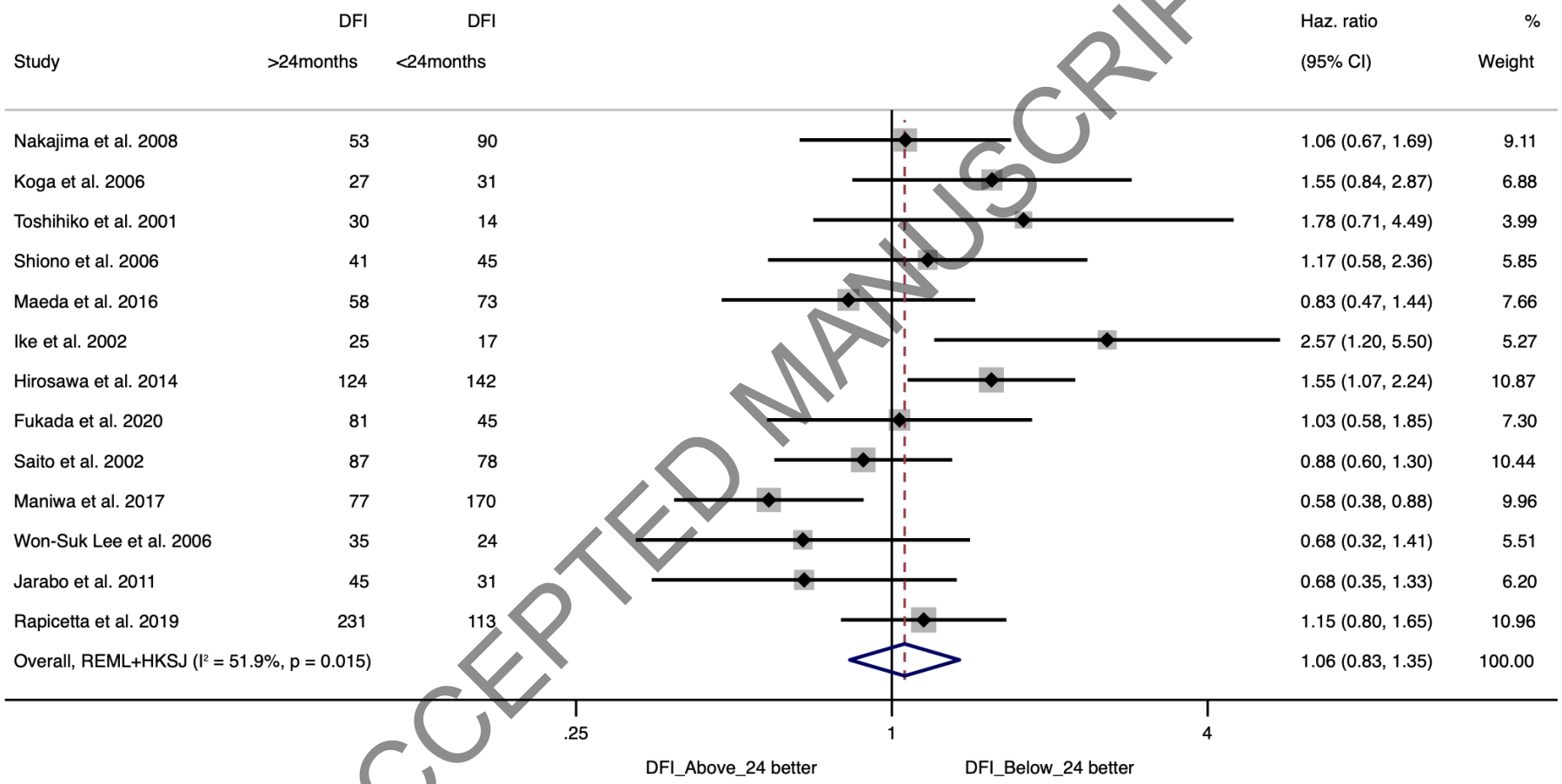
Central Image. Prognostic effect of Disease Free Interval (DFI) < / > 24months on 5-year post-operative survival following pulmonary metastasectomy.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the article screening process of the systematic review of the literature.

Figure 2. Prognostic effect of Disease Free Interval (DFI) < / > 24months on 5-year post-operative survival following pulmonary metastasectomy.

Figure 3. Prognostic effect of Synchronous or Metachronous lung metastasis diagnosis on 5-year post-operative survival following pulmonary metastasectomy.

Central image



NOTE: Weights are from random-effects model

Figure 2

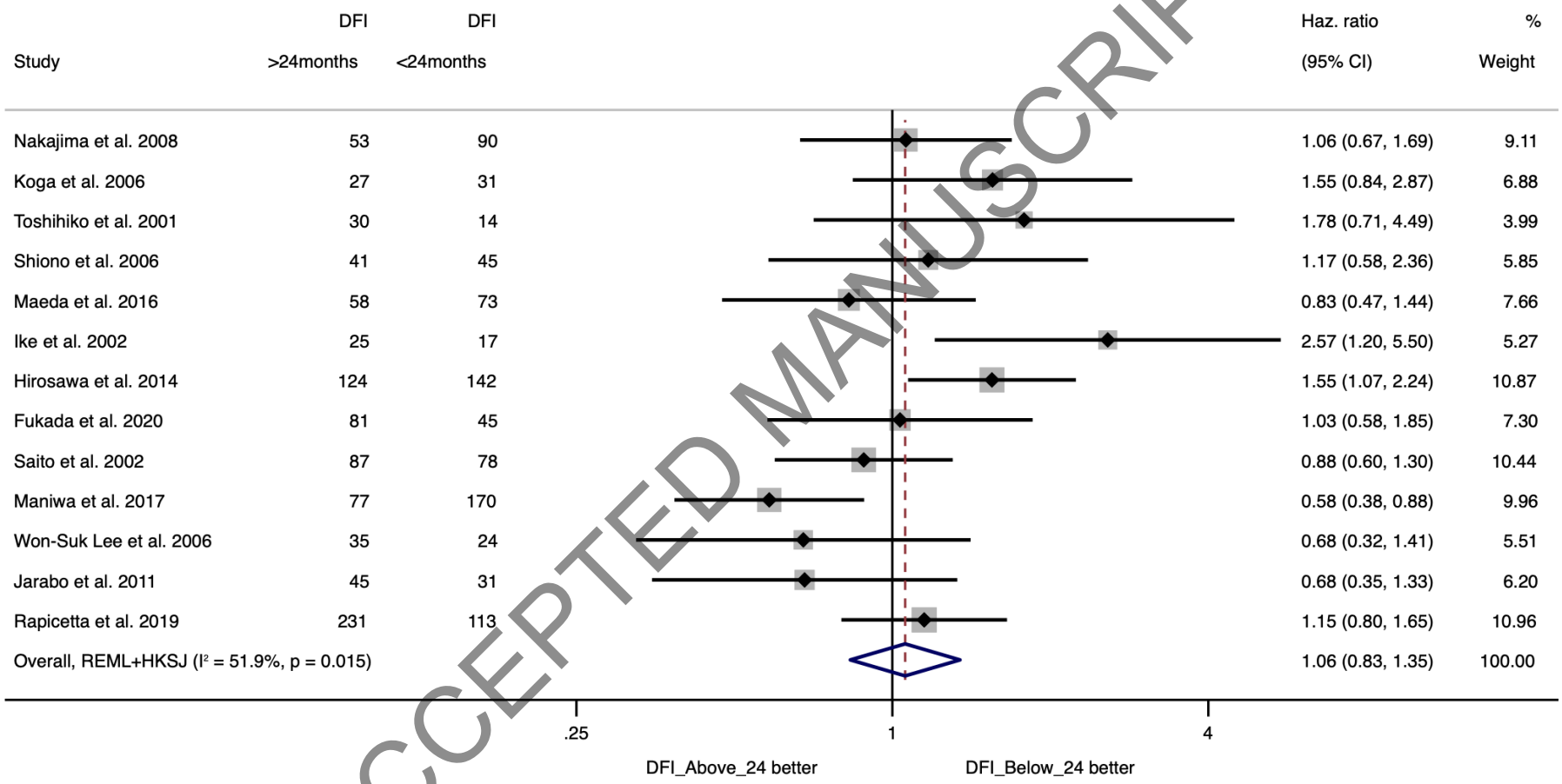


Figure 2.

Figure 3

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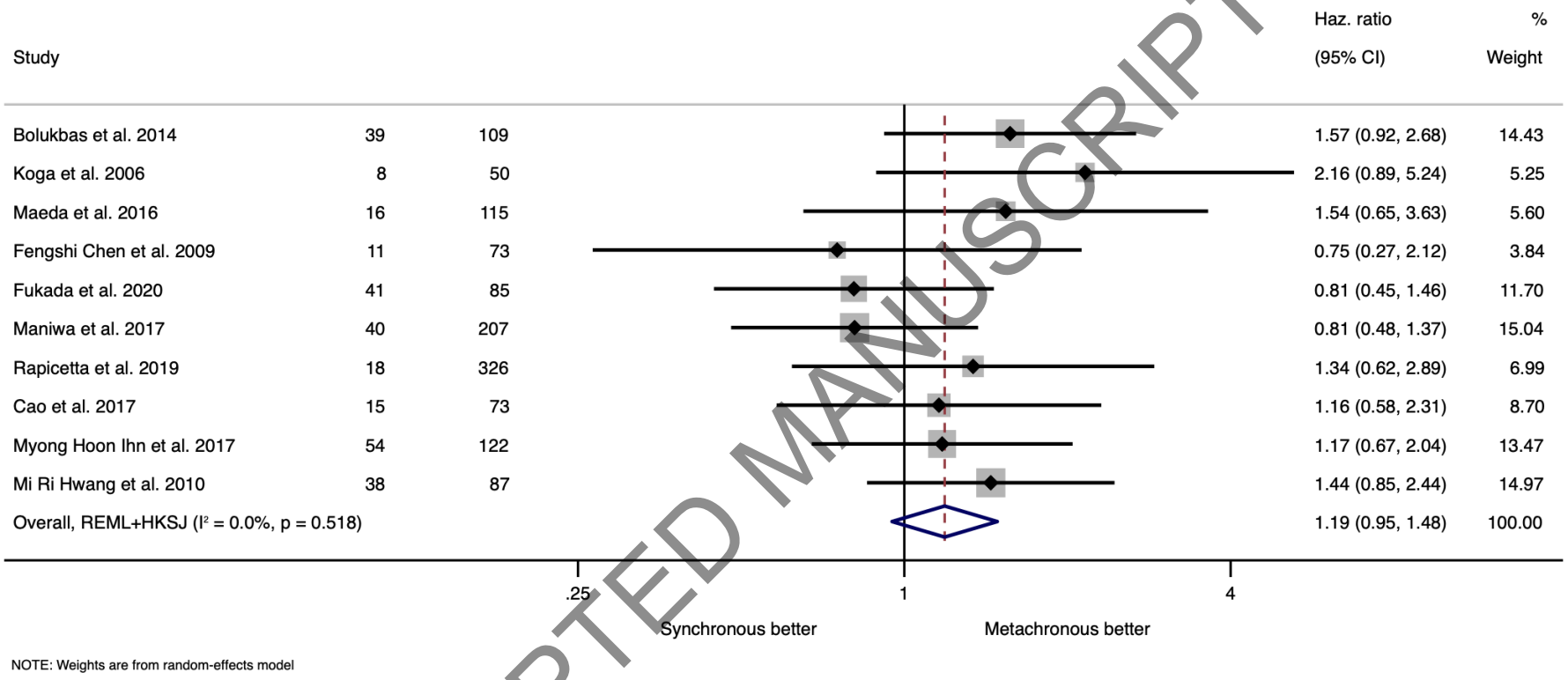

Figure 3.

Figure 1