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REVIEW

Prognostic impact of pleural effusion in patients with malignancy: A systematic review and meta-analysis

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Abstract

The exact role of pleural effusion in the prognosis of cancer patients remains unclear. We aimed to systematically review the prognostic value of pleural effusion in patients with cancer. We performed a systematic review and meta-analysis with a systematic literature search. All cohort studies with available overall survival (OS) and progression-free survival (PFS) results for patients with cancer with or without pleural effusion were included. The Mantel–Haenszel method was used to calculate the pooled hazard ratios (HRs) and 95% confidence intervals (CIs). Heterogeneity and publication bias were examined. Subgroup analysis and sensitivity analysis were performed. A total of 47 studies with 146,117 patients were included in the analysis. For OS, pleural effusion was a prognostic factor associated with a poor prognosis for patients with cancer (HR, 1.58, 95% CI, 1.43–1.75; I^2 94.8%). In the subgroup analysis, pleural effusion was a prognostic factor associated with poor survival for patients with lung cancer (HR, 1.44, 95% CI, 1.35–1.54; I^2 60.8%), hematological cancer (HR, 2.79, 95% CI, 1.63–4.77; I^2 29.4%) and other types of cancer (HR, 2.08, 95% CI, 1.43–3.01; I^2 55.1%). For PFS, pleural effusion was a prognostic factor associated with a poor prognosis for patients with cancer (HR, 1.61, 95% CI, 1.28–2.03; I^2 42.9%). We also observed that massive pleural effusion was a prognostic factor associated with a poorer prognosis compared to minimal pleural effusion. Pleural effusion had prognostic value in both OS and PFS of patients with cancer, except for patients with malignant pleural mesothelioma, regardless of whether the malignant effusion was confirmed histologically or cytologically. However, future evidence of other pleural effusion characteristics is still needed.

Yuan Yang and Juan Du authors contributed equally to the present work.

INTRODUCTION

Cancer is the second leading cause of death globally and was responsible for an estimated 9.6 million deaths in 2018.[1] Pleural effusion is a common complication in patients with cancer, and malignant pleural effusion—the discovery of malignant cells in pleural fluid and/or parietal pleura—is one of the most common types of pleural effusion. The occurrence of malignant effusion signifies disseminated or advanced disease and reduced life expectancy in patients with cancer.[2] Malignant effusion accounts for greater than 125,000 hospital admissions per year in the United States, with inpatient charges estimated to be greater than $5 billion per year.[3] Although any malignancy may involve the pleura, the most common causes of malignant effusion are lung cancer (37.5%), breast cancer (16.8%), and lymphoma (11.5%).[4] The important role of pleural effusion in the prognosis of cancer can be seen in the seventh edition of the TNM staging classification by the American Joint Committee on Cancer, in which its status was changed from T4 to M1a.[5] The mean survival of patients with cancer with malignant effusion ranges from 4 to 7 months and is dependent on the stage and type of the underlying malignancy.[6]

The prognostic value of pleural effusion in lung cancer has been revealed since 1990[7] and it has been demonstrated in many other cancer types, such as malignant pleural mesothelioma, ovarian cancer, hematologic malignancies, and even in thymic epithelial tumors and so on in the next years.[8-11] Most of the results are the same: pleural effusion is a prognostic factor associated with a poor prognosis for patients with cancer. There are also articles indicating that different characteristics of pleural effusion, such as volume and time of occurrence, have different prognostic value in patients with cancer.[12,13]The study by David et al. suggested that the prognosis of patients with cancer with malignant pleural effusion (MPE) was strongly associated with the amount of pleural effusion, independent of histology. However, Shang et al. found that the prognosis of patients with MPE is associated with gene mutations and treatment in specific cancer types.

We aim to systematically synthesize the published evidence on the associations between pleural effusion and the prognosis of patients with cancer. To our knowledge, no published study has systematically synthesized this evidence.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis aimed to reveal the prognostic value of pleural effusion in all patients with cancer. Five databases were searched covering the time from database creation to April 2, 2020: PubMed, Cochrane Library, Medline (accessed via OVID), Embase, and Web of Science. Our initial search items included "pleural effusion" and "malignant" and "prognosis" and related words. The specific search strategy is listed in Table S1. Our systematic review and meta-analysis were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[14]

Eligibility criteria

All prospective or retrospective cohort studies and case-control studies that mentioned the prognostic value of pleural effusion in cancer patients were enrolled after the initial screening. No language, publication data, or publication status was restricted. Adult patients with cancer aged above 18 years with or without pleural effusion were considered. Malignant effusion was identified when malignant cells were discovered in pleural fluid and/or parietal pleura. There were no restrictions on cancer types, treatment methods, or comorbidities with other illnesses. The exact inclusion criteria and exclusion criteria are listed below.

Inclusion criteria: (1) study population: patients with any cancer type; (2) indictor: pleural effusion, massive pleural effusion, and metachronous pleural effusion; (3) comparison: without pleural effusion, minimal pleural effusion, and synchronous pleural effusion; (4) outcomes: overall survival (OS) and progression-free survival (PFS); and (5) study type: prospective or retrospective cohort studies and case-control studies.

Exclusion criteria: (1) patients aged below 18 years; (2) reviews, comments, editorials, case reports, meeting abstracts, or corresponding letters; (3) full text unavailable in English; (4) insufficient information for data extraction; and (5) study population less than 30.

The methods were defined in advance in the original study protocol (Supplementary Materials).

Data extraction and quality assessment

Two teams of two reviewers (authors Y.Y. and D.J. plus W.Y.S. and K.H.Y.J.) independently searched the databases according to the search strategy. Disagreements between the two reviewer groups were resolved by consensus. When abstracts did not provide enough information, the full texts were assessed. We developed a data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction

template (https://cccrg.cochrane.org/author-resources). Two reviewers (authors Y.Y. and D.J.) independently extracted the data with the data extraction sheet. They cross-checked the data, and disagreements were resolved by discussion. Five authors were emailed because their papers did not provide enough information, but no one replied. Only Dr. Hricak answered for her article,[15] but that data were collected approximately 10 years ago and were no longer available. Therefore, we excluded those papers.

The following information was extracted from each included trial: (1) characteristics of the participants (including age, sex, nationality, and primary cancer type); (2) observation target (including with or without pleural effusion, massive or minimal pleural effusion, metachronous or synchronous pleural effusion); and (3) outcome measurements (OS and PFS). The Cox proportional hazards modeling results of hazard ratios (HRs) and 95% confidence intervals (CIs) of prognostic factors were extracted, and we applied Origin software (version 2020; https://www.originlab.com/) to digitize and extract key data from the published Kaplan–Meier curves. When HR, 95% CI, and Kaplan–Meier curves were not provided directly, the data extraction method was based on the method of Parmar et al.[16]

The quality of each study was assessed in accordance with the Newcastle–Ottawa Scale (NOS).[17] As all included studies were cohort studies, the scoring was based on the following items: (1) selection: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of the exposure, and demonstration that the outcome of interest was not present at the start of the study; (2) comparability: comparability of the cohorts on the basis of the design or analysis; and (3) outcome: assessment of the outcome, whether follow-up was long enough for outcomes to occur, and adequacy of the follow-up of cohorts. Two reviewers (authors Y.Y. and D.J.) independently assessed the risk of bias of each trial. They cross-checked the data and settled discrepancies by discussion.

Statistical analysis

We used the Mantel–Haenszel method to calculate the pooled HR and 95% CI with a random-effects model. Data were graphically displayed using forest plots. I^2 test was used to detect heterogeneity. The I^2 cutoffs 0 to 40%, 30% to 60%, 50% to 90%, and 75% to 100% represented low, moderate, substantial, and considerable heterogeneity, respectively.[18] To identify potential sources of heterogeneity, we performed subgroup analyses for cancer types (lung cancer, malignant pleural mesothelioma, hematologic malignancies, and other cancer types). Sensitivity analyses were performed to find the source of heterogeneity. Funnel plots and contour-enhanced meta-analysis funnel plots were used to examine publication bias. A two-sided p value less than 0.05 was considered to indicate statistical significance. The data analyses were performed using Stata software (version 15; https://www.stata.com/).

Patient and public involvement

There were no funds and no time allocated for patient and public involvement, so we were unable to involve patients. We invited patients to help us develop our dissemination strategy.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

RESULTS

Study selection and characteristics

The systematic review yielded 12,189 references from five electronic databases. Eventually, we identified 47 studies with a total of 146,117 patients that met our inclusion criteria.[7-13,15,19-57] The numbers of studies comparing the OS and PFS differences between patients with pleural effusion and patients without pleural effusion were 39 and nine, respectively. Seven studies evaluated the prognostic value of massive pleural effusion and minimal pleural effusion. Three studies evaluated the prognostic value of metachronous pleural infusion and synchronous pleural effusion. All 47 studies included in this systematic review were cohort studies. Figure 1 presents the PRISMA diagram of the study selection. The basic characteristics of all included studies are listed in Table 1 (more information is listed in Table S2).

Quality assessment of individual studies

The quality of each study was assessed in accordance with the NOS and the results are summarized in Table S3. The NOS scores of all involved studies were above six, which indicates a low risk of bias.

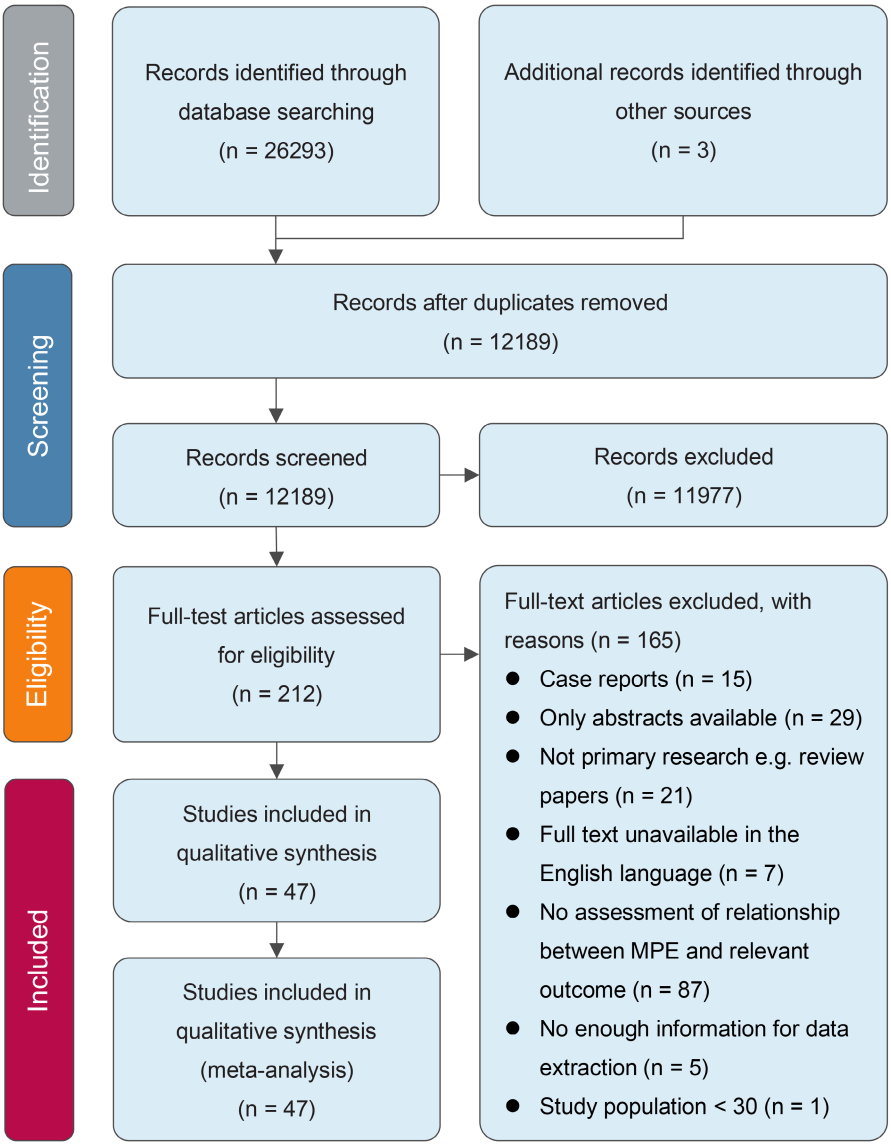

FIGURE 1 The PRISMA diagram for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MPE, malignant pleural effusion

Patients with or without pleural effusion, primary outcome: OS

In the 47 included studies, 39 studies reported OS as an outcome and evaluated the prognostic value of pleural effusion in patients with cancer. In these 39 studies, 24 were lung cancer studies, three were malignant pleural mesothelioma studies, five were hematologic malignancy studies, and seven were studies of other cancers (including 2 studies of ovarian cancer and 1 study each of hepatocellular carcinoma, thymic epithelial tumor, Askin-Rosai tumor, pulmonary Kaposi's sarcoma, and malignant superior vena cava syndrome). To prevent excessive heterogeneity, we performed a subgroup analysis considering the different cancer types.

Figure 2 shows the forest plot of the association between pleural effusion and OS subgrouped by cancer type. The pooled data demonstrated that pleural effusion was a prognostic factor associated with a poor prognosis for patients with cancer (HR, 1.58, 95% CI,1.43–1.75). In the subgroup analysis, pleural effusion was a prognostic factor associated with a poor prognosis for patients with lung cancer (HR, 1.44, 95% CI, 1.35–1.54), patients with hematologic malignancy (HR, 2.79, 95% CI, 1.63–4.77), and patients with other types of cancer (HR, 2.08, 95% CI, 1.43–3.01). Only in patients with malignant pleural mesothelioma was pleural effusion not a prognostic factor (HR, 1.72, 95% CI, 0.79–3.71). Heterogeneity testing revealed considerable heterogeneity (I^2 = 94.8%, $p < 0.001$) for all 39 studies. In the subgroup analysis, the lung cancer subgroup had substantial heterogeneity (I^2 = 60.8%, $p < 0.001$), the malignant pleural mesothelioma subgroup had considerable heterogeneity (I^2 = 91.9%, $p < 0.001$), the hematologic malignancy subgroup had low heterogeneity (I^2 = 29.4%, $p = 0.225$), and the other cancers subgroup had moderate heterogeneity (I^2 = 55.1%, $p = 0.038$).

TABLE 1 Baseline characteristics of the included studies

Study	Year	Country	Age	Sex	Cancer types	Marker	Outcome	Sample size
Albain et al.[7]	1990	United States	NA	NA	Lung cancer	PE vs. Non-PE	OS	2580
Wigren et al.[19]	1992	Finland	65 (36–84)	Mixed (92% male)	NSCLC	PE vs. Non-PE	OS	279
					NSCLC	Massive PE vs. minimal PE	OS	
Morel et al.[20]	1993	France	51 (22–84)	Mixed (49% male)	Follicular lymphoma	PE vs. Non-PE	OS	91
Coen et al.[21]	1995	Belgium	Median 69	Mixed (94.14% male)	NSCLC	PE vs. Non-PE	OS	317
Sugiura et al.[22]	1997	Japan	NA	Mixed (67.5% male)	NSCLC	PE vs. Non-PE	OS	197
Natio et al.[23]	1997	Japan	22–88	Mixed (72.7% male)	NSCLC	PE vs. Non-PE	OS	708
Hannon et al.[24]	1998	United Kingdom	37 (31–45)	Male	Pulmonary Kaposi's sarcoma	PE vs. Non-PE	OS	80
Bonnefoi et al.[9]	1999	United Kingdom	20–86	Female	Epithelial ovarian cancer	PE vs. Non-PE	OS	192
					Epithelial ovarian cancer	PE vs. Non-PE	PFS	
Maria et al.[25]	2000	United States	NA	Mixed (72% male)	NSCLC	PE vs. Non-PE	OS	1999
Jime´nez et al.[12]	2005	Spain	63.3 ± 17.1(massive PE); 63.4 ± 17.4 (minimal PE)	NA	MPE	Massive PE vs. minimal PE	OS	434
Yakushiji et al.[11]	2008	Japan	24–80	Mixed (49.3% male)	Thymic epithelial tumor	PE vs. Non-PE	OS	75
Tanrikulu et al.[8]	2010	Turkey	NA	Mixed (59.8% male)	MPM	PE vs. Non-PE	OS	363
Hyodo et al.[26]	2010	Japan	63 + 12	Mixed (51.74% male)	Lung, stomach, breast, panceas, colorectal and other cancer	Massive PE vs. minimal PE	OS	406
Mironov et al.[15]	2011	United States	37–96	Female	Epithelial ovarian cancer	PE vs. Non-PE	OS	203
Laskar et al.[27]	2011	India	3–60	Mixed (70.2% male)	Askin-Rosai tumor	PE vs. Non-PE	OS	104
Lee et al.[28]	2011	Korea	65 ± 10	Mixed (74% male)	NSCLC	PE vs. Non-PE	OS	156
Kim et al.[29]	2011	Korea	60 ± 12	Mixed (58.1% male)	NSCLC	PE vs. Non-PE	OS	86
Morgensztern et al.[30]	2012	United States	21–101	Mixed (54.4% male)	NSCLC	PE vs. Non-PE	OS	57685
Wu et al.[13]	2013	China	27.9–95.5	Mixed (45.5% male)	Lung adenocarcinoma	Metachronous vs. Synchronous MPE	OS	448
Ryu et al.[31]	2014	South Korea	67	Mixed (73.5% male)	NSCLC	PE vs. Non-PE	OS	2061
					NSCLC	Massive PE vs. minimal PE	OS	
Hunter et al.[10]	2014	United States	NA	Mixed (55% male)	Hodgkin lymphoma	PE vs. Non-PE	OS	110

TABLE 1 (Continued)

Study	Year	Country	Age	Sex	Cancer types	Marker	Outcome	Sample size
Ulas et al.[32]	2014	Turkey	22–85	Mixed (87.66% male)	NSCLC	PE vs. Non-PE	OS	462
Previs et al.[33]	2014	United States	59 (19–85)	Female	Ovarian cancer	PE vs. Non-PE	PFS	312
Porcel et al.[34]	2015	Spain	58–78	Mixed (77% male)	Lung cancer	PE vs. Non-PE	OS	537
					Lung cancer	Massive PE vs. minimal PE	OS	
					Lung cancer	Metachronous vs. Synchronous MPE	OS	
Liu et al.[35]	2015	China	38–80	Mixed (61.25% male)	NSCLC	PE vs. Non-PE	OS	80
Qiao et al.[36]	2015	China	Median 75	Mixed (67.5% male)	Lung cancer	PE vs. Non-PE	OS	160
Ryu et al.[37]	2016	South Korea	35–89	Mixed (90% male)	SCLC	PE vs. Non-PE	OS	360
					SCLC	Massive PE vs. minimal PE	OS	
Uchiyama et al.[38]	2017	Japan	17–87	Mixed (76.1% male)	Hepatocellular carcinoma	PE vs. Non-PE	OS	330
Porcel et al.[39]	2017	Spain	55–81	Mixed (48.37% male)	Hematological and ovarian cancer	Metachronous vs. Synchronous MPE	OS	72
Saito et al.[40]	2017	Japan	70 (41–90)	Mixed (76.3% male)	Waldenström macroglobulinemia	PE vs. Non-PE	OS	93
					Waldenström macroglobulinemia	PE vs. Non-PE	PFS	
Taniguchi et al.[41]	2017	Japan	72 (39–91)	Mixed (28.7% male)	NSCLC	PE vs. Non-PE	OS	178
					NSCLC	PE vs. Non-PE	PFS	
Paajanen et al.[42]	2018	Finland	43–89	Mixed (86% male)	MPM	PE vs. Non-PE	OS	161
Watanabe et al.[43]	2018	United States	35–86	Mixed (43% male)	Lung adenocarcinoma	PE vs. Non-PE	PFS	72
Fan et al.[44]	2018	China	63.2 ± 10.7	Mixed (71.7%male)	SCLC	PE vs. Non-PE	OS	120
Hu et al.[45]	2018	China	25 (18–61)	Mixed (81.4% male)	T-lymphoblastic lymphoma	PE vs. Non-PE	OS	59
Yoshimura et al.[46]	2019	Japan	38–88	Mixed (42% male)	NSCLC	PE vs. Non-PE	OS	50
					NSCLC	PE vs. Non-PE	PFS	
Porcel et al.[47]	2019	Spain	52–76	Mixed (57% male)	Diffuse large B-cell lymphomas	PE vs. Non-PE	OS	185
					Diffuse large B-cell lymphomas	Massive PE vs. minimal PE	OS	
Shibaki et al.[48]	2019	Japan	30–83	Mixed (68% male)	NSCLC	PE vs. Non-PE	OS	252
					NSCLC	PE vs. Non-PE	PFS	

(Continues)

TABLE 1 (Continued)

Study	Year	Country	Age	Sex	Cancer types	Marker	Outcome	Sample size
Chen et al.[49]	2019	China Taiwan	Median 64.0	Mixed (61.9% male)	Lung adenocarcinoma	PE vs. Non-PE	OS	4389
Shojaee et al.[50]	2019	United States	19–101	Mixed (50.2% male)	SCLC	PE vs. Non-PE	OS	68443
Hu et al.[51]	2019	China	60 (35–84)	Mixed (56% male)	Lung adenocarcinoma	PE vs. Non-PE	OS	137
Bibby et al.[52]	2019	United Kingdom	64 (40–93)	Mixed (85.6% male)	MPM	PE vs. Non-PE	OS	229
Tamir et al.[53]	2019	Netherlands	59 (18–90)	Mixed (54% male)	Malignant Superior Vena Cava Syndrome	PE vs. Non-PE	OS	127
Adachi et al.[54]	2020	Japan	70 (64–76)	Mixed (69.6% male)	NSCLC	PE vs. Non-PE	PFS	296
Pantano et al.[55]	2020	Italy	34–90	Mixed (68% male)	NSCLC	PE vs. Non-PE	DSS[a]	294
Kim et al.[56]	2020	Korea	60.6 ± 12.5	Mixed (52.9% male)	NSCLC	PE vs. Non-PE	OS	104
Ng et al.[57]	2020	China	68.1 (40–91)	Mixed (48.9% male)	Lung adenocarcinoma	PE vs. Non-PE	PFS	41

Abbreviations: DSS, disease-specific survival; MPE, malignant pleural effusion; MPM, malignant pleural mesothelioma; NA, not available: NSCLC, non-small-cell lung cancer; OS, overall survival; PE, pleural effusion; PFS, progression-free survival; SCLC, small cell lung cancer.

[a]To ensure the integrity of the data, we included DSS in the OS group. After the sensitivity analysis, this study did not show apparent heterogeneity with OS studies.

To find the source of heterogeneity in the lung cancer subgroup, we separately combined the data extracted by different data extraction methods (Figure S1). The I^2 of the data extracted from the Cox regression model and calculated based on other data was below 50%, but it was still above 50% for the data extracted from the Kaplan–Meier curve. The sensitivity analysis demonstrated that individual lung cancer studies did not significantly influence the pooled results (Figure S2). The contour-enhanced meta-analysis funnel plot of the HR for OS of patients with lung cancer is presented in Figure S3 and revealed a possible publication bias.

In most instances, the presence of pleural effusion in patients with cancer probably indicates that cancer cells had spread to the pleural cavity. However, Canto et al.'s study found that 17% of pleural effusions analyzed in patients with cancer were determined to be unrelated to tumor invasion of the pleura (e.g., postsurgery, pneumonia, or heart failure).[58] In the 39 studies included in our analysis, 13 of them demonstrated that malignant effusion affected the prognosis in cytological or histological examinations, but the others only showed that pleural effusion affected the prognosis and did not mention the type of pleural effusion. Therefore, we performed an analysis subgrouped by malignant effusion or pleural effusion (Figure 3). The pooled data demonstrated that malignant effusion was a prognostic factor associated with a poor prognosis for patients with cancer (HR, 1.67, 95% CI, 1.42–1.95), and there was a similar finding for the pleural effusion subgroup (HR, 1.46, 95% CI, 1.32–1.61).

The prevalence of malignant pleural effusion requiring personalized management continues to increase worldwide, and despite technological advances, treatment remains resource-intensive.[59] Thus, the burden of the management of malignant pleural effusion is an important consideration. The countries of the patients may reflect the local economic levels and the quality of accessible medical care. In this context, subgroup analyses were performed by categorizing subgroups by country (Figure 4). The pooled data demonstrated that malignant effusion was a prognostic factor for patients with cancer and was associated with a poor prognosis in all countries except Korea (HR, 1.38, 95% CI, 0.99–1.92). In the subgroup analysis of malignant effusion, there were significant subgroup differences between the patients from different countries (test for subgroup differences: $p = 0.034$).

Patients with or without pleural effusion, secondary outcome: PFS

For the nine studies that reported the prognostic value of pleural effusion for PFS in patients with cancer, the pooled

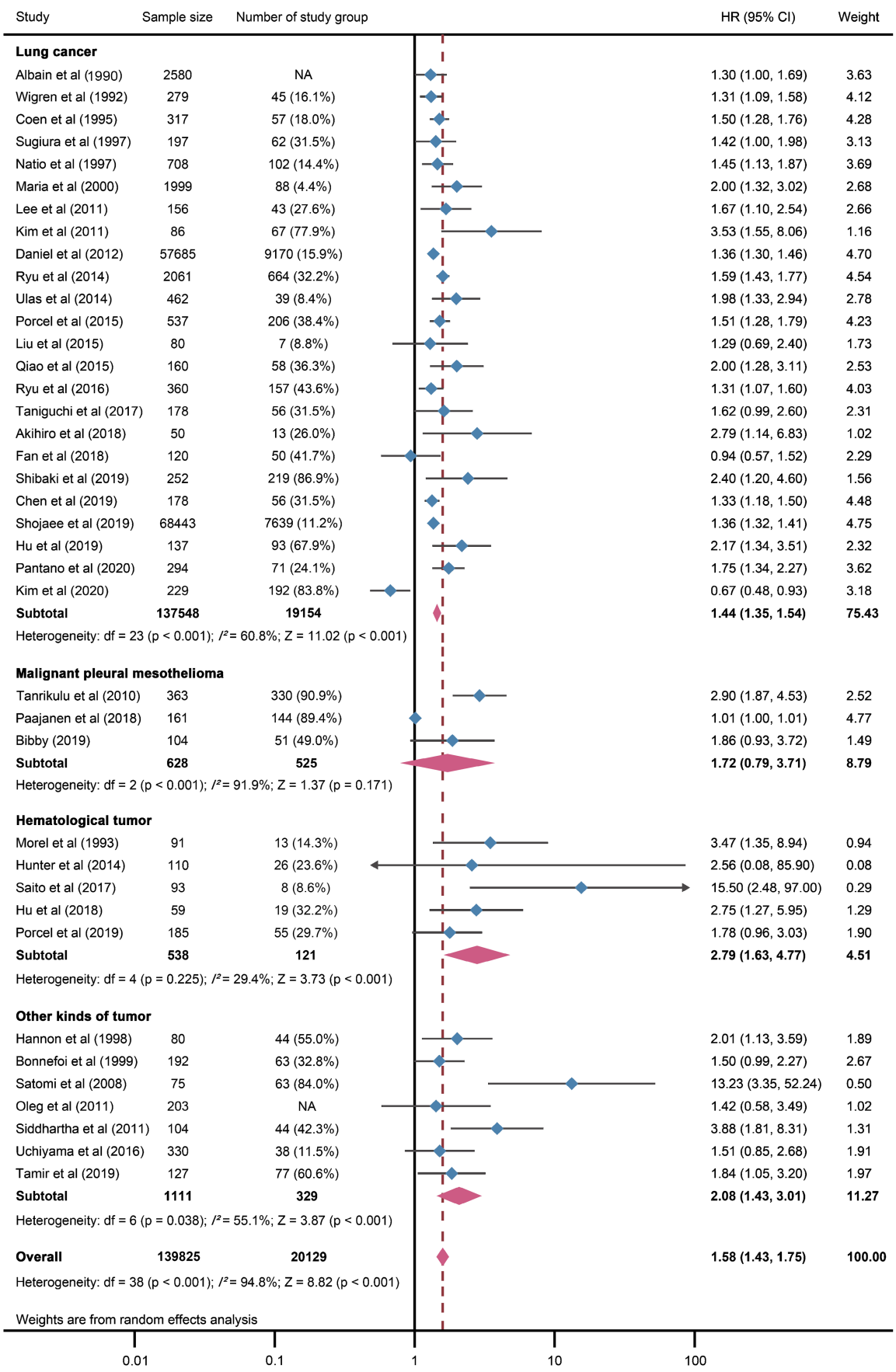

FIGURE 2 Forest plot of the hazard ratios of pleural effusion for overall survival in patients with cancer, subgrouped by tumor type. CI, confidence interval; HR, hazard ratio

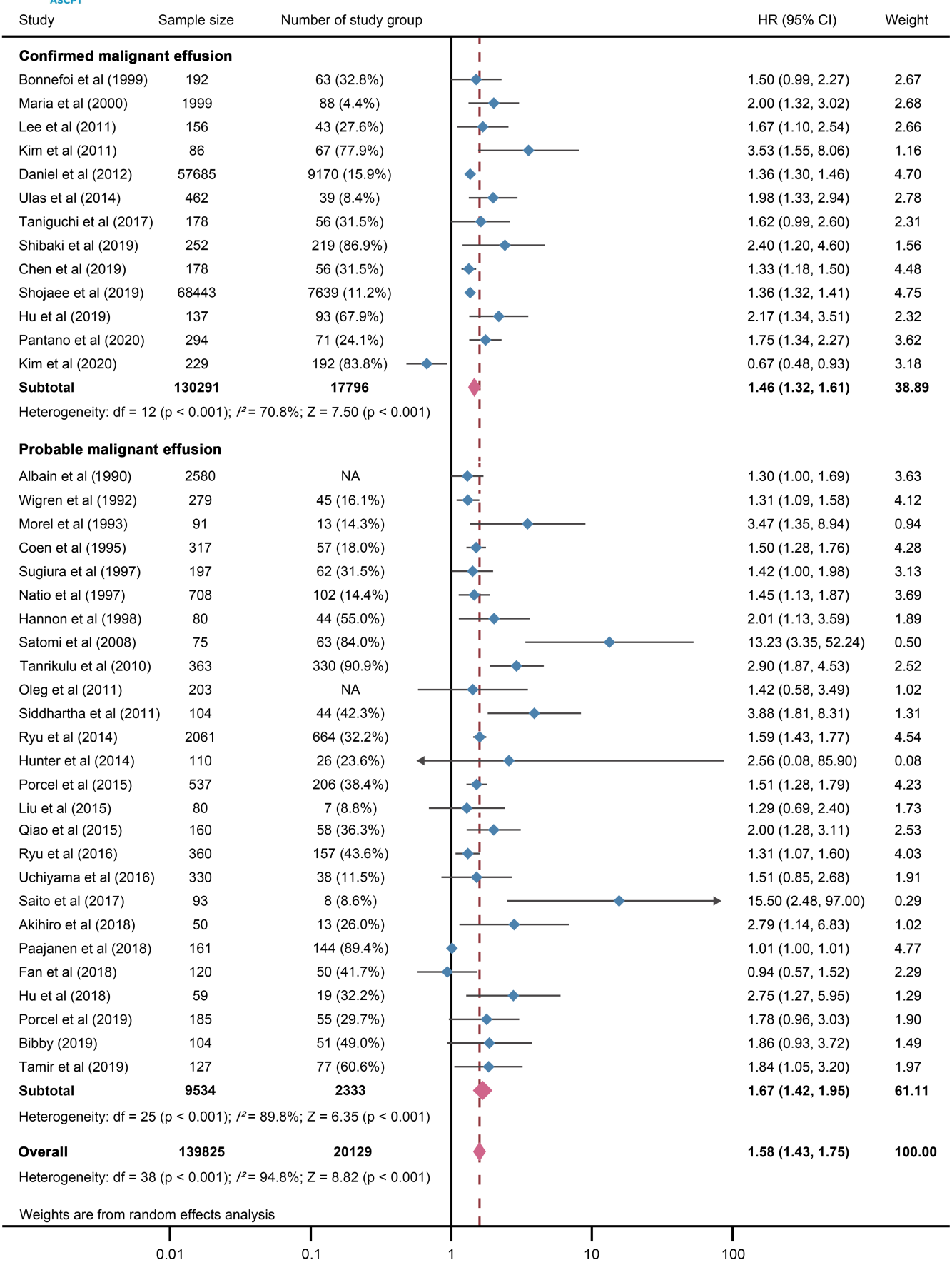

FIGURE 3 Forest plot of the HRs of pleural effusion for overall survival in patients with cancer, subgrouped by whether malignant effusion was confirmed histologically or cytologically. CI, confidence interval; HR, hazard ratio; NA, not available

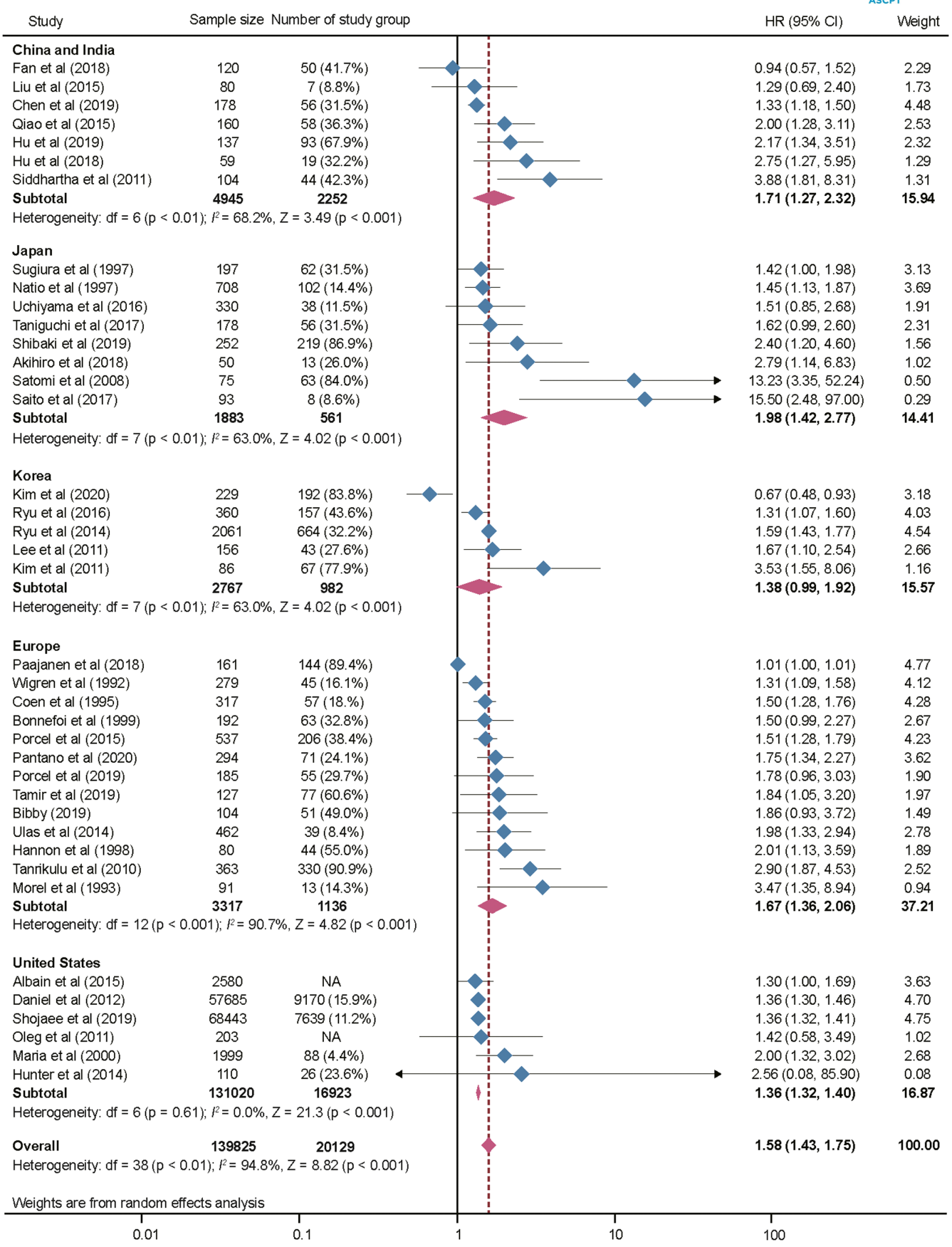

FIGURE 4 Forest plot of the hazard ratios of pleural effusion for overall survival in patients with cancer, subgrouped by country. CI, confidence interval; HR, hazard ratio; NA, not available

data demonstrated that pleural effusion was a prognostic factor associated with a poor prognosis for PFS in patients with cancer (HR, 1.61, 95% CI, 1.28–2.03). Forest plots are shown in Figure 5. Heterogeneity testing revealed that the prognostic value of pleural effusion for PFS had moderate heterogeneity (I^2 = 42·9%, p = 0.081). The contour-enhanced meta-analysis funnel plot of the HR for PFS is presented in Figure S4 and revealed a possible publication bias.

Patients with massive or minimal pleural effusion

Seven studies reported the prognostic value of massive pleural effusion compared to minimal pleural effusion. Although the cutoffs of massive and minimal pleural effusion differed (1 cm, 2 cm, or 200 ml), the pooled data still demonstrated that massive pleural effusion is a prognostic factor associated with a poor prognosis (HR, 1.32, 95% CI, 1.13–1.55). Forest plots are shown in Figure 6. Heterogeneity testing revealed that these seven studies had moderate heterogeneity (I^2 = 58.0%, p = 0.027). The contour-enhanced meta-analysis funnel plot of this group of studies is presented in Figure S5 and revealed a possible publication bias.

Patients with metachronous or synchronous pleural effusion

Only three articles discussed the prognostic value of metachronous pleural effusion compared to synchronous pleural effusion. The pooled data demonstrated that metachronous pleural effusion is not a prognostic indicator in patients with cancer (HR, 1.29, 95% CI, 0.60–2.76), because two articles considered it a risk factor and one considered it a protective factor. Forest plots are shown in Figure S6. Heterogeneity testing revealed that these three studies had considerable heterogeneity (I^2 = 93.3%, p < 0.001).

DISCUSSION

There is a general consensus that the occurrence of pleural effusion in patients with cancer signifies metastasis and reduces life expectancy.[60] However, the exact role of pleural effusion in the prognosis of patients with cancer remains unclear. This study systematically summarized the association between pleural effusion and the prognosis of patients with cancer. Our main findings indicate that, regardless of whether malignant effusion is confirmed histologically or cytologically, pleural effusion has prognostic value in patients with cancer except those with malignant pleural mesothelioma. It is a prognostic risk factor in both OS and PFS. Patients with massive pleural effusion have a worse prognosis than patients with minimal pleural effusion. The time of discovery of pleural effusion is not a prognostic factor for patients with cancer.

The prognosis of patients with minimal pleural effusion is better than that of patients with massive pleural effusion, which may suggest that if we can prevent a small amount of pleural effusion from progressing to a large amount of pleural effusion by appropriate methods or if a large amount of pleural effusion can be reduced to a lower

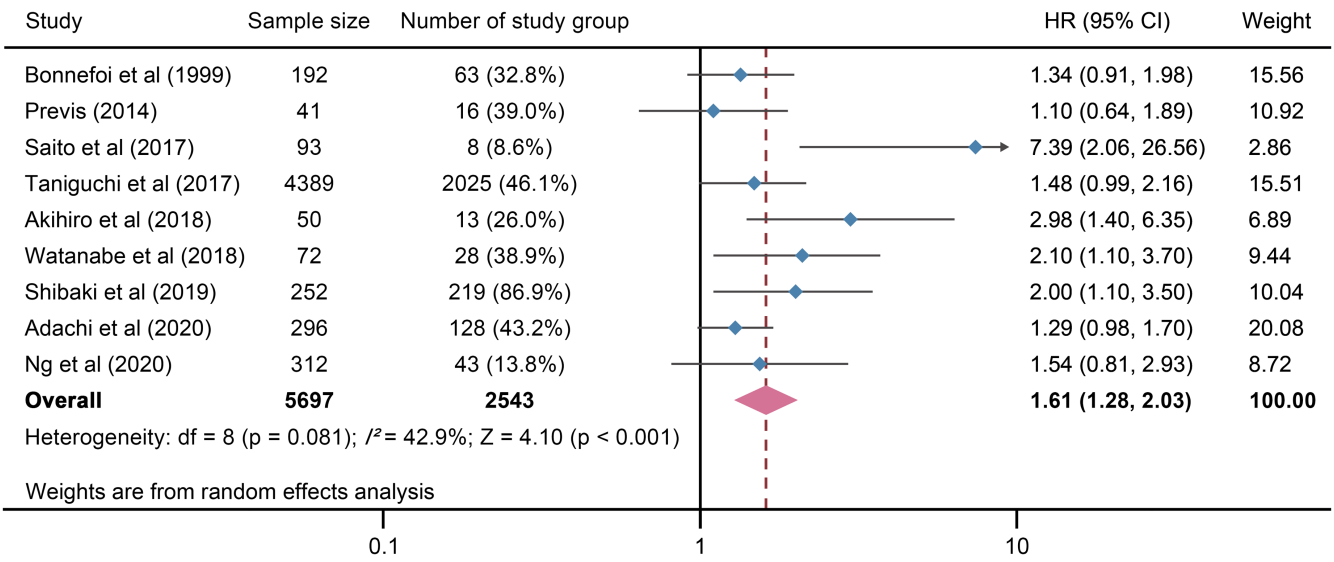

FIGURE 5 Forest plot of the hazard ratios of pleural effusion for progression-free survival in patients with cancer. CI, confidence interval; HR, hazard ratio

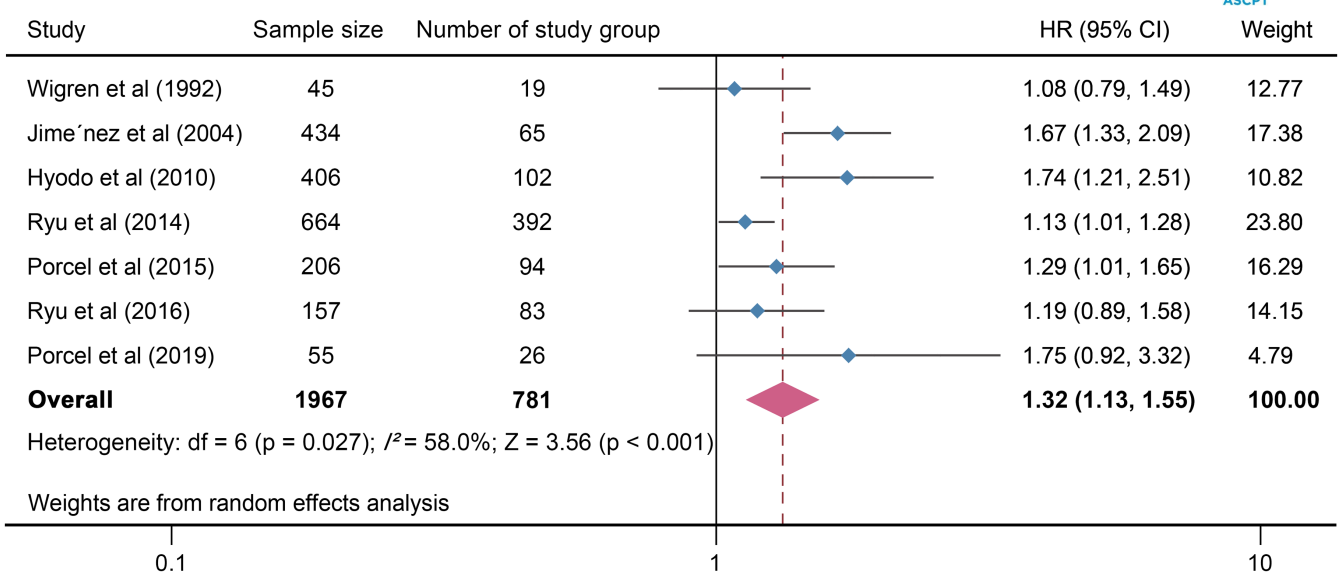

FIGURE 6 Forest plot of the hazard ratios of massive pleural effusion compared to minimal pleural effusion in patients with cancer. CI, confidence interval; HR, hazard ratio

amount, we may improve patient outcomes. Current management methods for pleural effusion include pleurodesis, indwelling pleural catheters, and surgical options. The influence of the management of pleural effusion on the prognosis of patients should be considered according to the amount of pleural effusion to select the appropriate management method and provide a basis for personalized MPE management.

When we explored the relationship between pleural effusion and OS, heterogeneity testing detected significant heterogeneity. Even when we performed the subgroup analysis, heterogeneity still existed in the lung cancer subgroup, the malignant pleural mesothelioma subgroup, and the other cancers group. Then, we separately combined the data extracted by different data extraction methods in the lung cancer subgroup (Figure S1) and found that the heterogeneity was mainly concentrated in the data extracted from the Kaplan–Meier curve. As most of the Kaplan–Meier curves were not adjusted, this may be one of the reasons for heterogeneity. We also performed a sensitivity analysis in the lung cancer subgroup (Figure S2). Although the sensitivity analysis showed that individual studies did not significantly influence the pooled results statistically, two studies showed relatively large impacts on data integration.[30,50] The reason for this phenomenon may be the large study population in these two studies (57,685 and 68,443, respectively). Another reason for the heterogeneity in the lung cancer subgroup may be the different pathology types of each study, which included non-small cell lung cancer, small-cell lung cancer, and lung adenocarcinoma. Different pathologies may lead to different prognoses.[61] In addition, the result of Kim et al.[56] is completely in contrast with other studies. The contrary result may have been caused by a smaller control group, which only included patients with dry pleural dissemination non-small cell lung cancer.

The heterogeneity in the malignant pleural mesothelioma subgroup may have been caused by the small number of studies ($n = 3$). In the other cancer type subgroup, the heterogeneity mainly came from the different cancer types. Although heterogeneity existed, the result still suggested that pleural effusion may have prognostic value and is associated with poor survival in all cancer types. This opinion was reinforced by the results of the PFS analysis.

By analyzing subgroups of patients with a positive cytological or histological diagnosis of malignant pleural effusion and patients with an unconfirmed diagnosis, we found that whether malignant effusion was clearly diagnosed or not, pleural effusion had prognostic value in tumor patients. In the group analysis by country, there were significant subgroup differences between the patients from different countries, indicating that the country of the patients might lead to significant heterogeneity in the overall analysis.

In the analysis of massive and minimal pleural effusion, different cutoff values may be the reason for heterogeneity. However, the trend was consistent. This result affirms that a larger pleural effusion is more dangerous than a smaller pleural effusion. The heterogeneity may also be caused by the small study number or the different cancer types. In the analysis of metachronous and synchronous pleural effusion, no difference in OS was observed in the combined result. The heterogeneity may be caused by the small study number or the different trend results of each study.

Publication bias is a common problem in meta-analyses.[62] The reason for publication bias is that researchers tend to report positive results rather than negative results.[63] In our meta-analysis, the funnel plots and contour-enhanced meta-analysis funnel plots implied possible publication bias. To address this problem, we tried to involve all qualified studies, but publication bias cannot be avoided. The existence of publication bias makes it impossible for us to include all relevant studies despite having sufficient retrieval strategies and means. We should note that publication bias may overestimate the impact of pleural effusion on prognosis, leading to errors in individual clinical treatment and health decisions.

There are several limitations to this study. First, due to the limited number of studies analyzed, this paper did not focus on some major characteristics of pleural effusion, such as bilateral or unilateral pleural effusion and bloody or non-bloody pleural effusion. Second, we included only pooled data; case studies of individual patients were not included in the analysis. In addition, the OS and PFS of patients with cancer are easily influenced by comorbidities of systemic diseases, medications, and nutritional status, which were not discussed in this paper. Future studies should focus on the general status of patients, such as complications, patient nutrition, medications, and the major characteristics of pleural effusion, such as bloody or non-bloody pleural effusion and unilateral or bilateral pleural effusion, to better understand the prognostic value of pleural effusion for patients with cancer.

In conclusion, regardless of whether malignant effusion was confirmed histologically or cytologically, pleural effusion had prognostic value and was associated with a poor prognosis for patients with cancer except for those with malignant pleural mesothelioma. It is a prognostic risk factor in both OS and PFS. Patients with massive pleural effusion have a worse prognosis than patients with minimal pleural effusion. The time of discovery of pleural effusion is not a prognostic factor for patients with cancer.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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