REVIEW

Prognostic biomarkers of malignant patients with pleural effusion: a systematic review and meta-analysis

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Abstract

Background: Pleural effusion is a common clinical problem in patients with cancer. We aimed to summarize all the known prognostic indicators of malignant pleural effusion.

Methods: We did a systematic review and meta-analysis with a systematic literature search. All prospective or retrospective cohort studies that estimated the prognostic factors of malignant pleural effusion were enrolled. Mantel–Haenszel method was used to calculate the pooled hazard ratio (HR) and 95% confidence interval (CI).

Results: Eventually, we identified 82 studies with a total of 10,748 patients that met our inclusion criteria. The LENT score showed a good prognostic value (HR 1.97, 95% CI 1.67–2.31) so did the LENT score item. In addition, clinical parameters like stage (HR 1.68, 95% CI 1.25–2.25), distant metastasis (HR 1.62, 95% CI 1.38–1.89), EGFR mutation (HR 0.65, 95% CI 0.56–0.74), serum biological parameters like hemoglobin (HR 1.56, 95% CI 1.17–2.06), albumin (HR 1.71, 95% CI 1.25–2.34), C-reaction protein (HR 1.84, 95% CI 1.49–2.29), VEGF (HR 1.70, 95% CI 1.18–2.43) and pleural effusion biological parameters like PH (HR 1.95, 95% CI 1.46–2.60), glucose (HR 1.75, 95% CI 1.18–2.61), VEGF (HR 1.99, 95% CI 1.67–2.37), and survivin (HR 2.90, 95% CI 1.17–7.20) are also prognostic factors for malignant pleural effusion.

Conclusions: For malignant pleural effusion, LENT score and its items are valuable prognostic biomarkers, so do the clinical parameters like stage, distant metastasis, EGFR mutation, the serum biological parameters like hemoglobin, albumin, C-reaction protein, VEGF and the pleural effusion biological parameters like PH, glucose, VEGF and survivin.

Keywords: Pleural effusion, Cancer, Prognosis, Systematic review, Meta-analysis

Introduction

Pleural effusion is a common problem in many diseases especially in cancer. It occurs as a result of in situ pleural involvement and/or metastatic malignancy in the pleural cavity resulting in increased vascular permeability, production of excess fluid in excess of lymphatic reabsorption capacity, and/or disruption of lymphatic reabsorption capacity causing fluid accumulation in the pleural cavity [1]. It accounts for greater than 125,000 hospital admissions per year in the United States and estimated inpatient costs of greater than $5 billion per year [2]. The occurrence of pleural effusion in patients with malignancy always indicates disseminated or advanced disease [3]. In lung cancer, it upstages the severity of illness to stage IV [4] and significantly reduces life expectancy in non-small cell lung cancer [5]. The average survival of malignant pleural effusions (MPE) ranges from 4 to 7 months and is dependent on the stage and type of the underlying malignancy [6]. Increasing importance is placed on slowing down disease progression by improving risk factors. However, the factors that
define malignant progression and mortality in MPE are poorly understood.

The LENT scoring system is the first validated prognostic score in MPE. It predicts patients’ survival on the basis of tumor type, pleural fluid lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group Performance Status (ECOG PS), and blood neutrophil-to-lymphocyte ratio (NLR) and predicts survival with significantly better accuracy than ECOG PS alone [7]. Another prognostic model for MPE is the PROMISE score which combines biological and clinical parameters to accurately estimate 3-month mortality [8]. The modified LENT score was based on LENT score replacing the “tumor type” score of 2 with 0 in patients with lung adenocarcinoma to illustrate that the actual survival in patients having MPE from lung adenocarcinoma was higher than predicted by the LENT score [9]. A new prognostic model—SELECT prognostication model was proposed recently with high accuracy at identifying patients with high probability of survival at 90 days an Asian population [10]. Notably, EGFR mutations were included in prediction model for the first time. These findings are consistent with our meta-analysis that EGFR is a protective factor for lung cancer. In addition, minimal pleural effusion itself is also an important prognostic factor of worse survival, especially in early-stage malignant disease [11]. Our group has systematically studied the prognostic role of pleural effusion in malignancy and found that whether malignant effusion is clearly diagnosed with cytological or historical examination, pleural effusion is a prognostic factor associated with a poor prognosis for cancer patients. Thus, capturing clinical parameter biomarkers, plasma biomarkers and pleural effusion biomarkers are increasingly important.

We aim to systematically synthesize the published evidence on the associations between the prognostic biomarkers and clinical outcomes in patients with malignant pleural effusion to provide a new insight for development of scoring systems. To our knowledge, no published study has thoroughly and systematically summarized these evidences.

Methods

Search strategy and selection criteria

We conducted a systematic review and meta-analysis to assess the associations between the prognostic factors and clinical outcomes in malignant patients with pleural effusion. The search flow diagram for this meta-analysis is shown in Fig. 1. Databases searched included PubMed, Cochrane Library, Medline (accessed via OVID), Embase, and Web of Science, covering all dates from the creation of each database up to April 2, 2020. The index terms included “pleural effusion”, “malignant”, and “prognosis”, as well as the related words. Additional file 1: eTable 1 presents the detailed search strategy. Additional studies were identified by searching the list of references of included studies, as well as previous relevant meta-analysis and systematic reviews. This meta-analysis was carried out following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12].

Eligibility criteria

We enrolled prospective or retrospective cohort studies in English that estimated the association between prognostic factors and clinical outcomes in malignant patients with pleural effusion. There were no restrictions on studies with respect to settings, tumor types, or comorbidity types. Inclusion criteria were as follows: (1) study population: patients diagnosed with any type of malignancy and pleural effusion; (2) target: assessing a relevant biomarker; (3) outcomes: overall survival (OS), progression-free survival (PFS); (4) study type: prospective or retrospective cohort studies. The exclusion criteria included (1) studies involving infants, children and adolescents (2) no clearly reported diagnostic criteria for malignant tumor or pleural effusion; (3) narrative reviews, comments, editorials, case reports, meeting abstracts, guidelines or corresponding letters; and (4) full-text paper unavailable in English; (5) sample size < 20.

The methods were defined in advance in the original study protocol (Additional file 1, pp 1–2).

Data extraction and quality assessment

Two authors (YY and DJ) independently screened the title and abstract of the literature retrieved from the databases by the search strategy. Then YY and DJ independently reviewed the full text of articles and assessed articles for eligibility according to the inclusion criteria. Disagreements between the two authors were settled by arbitration of the principal investigator. Two authors extracted data from included studies using a standardized form based on the Cochrane Consumers and Communication Review Group’s data extraction template. The data extracted by the two authors was cross-checked and differences were resolved by checking the original article. Where data were not enough to extract, the corresponding authors were contacted and asked to provide data.

Data extracted included: (1) clinical characteristics (including age, gender, country, publication year, sample size, and primary tumor type); (2) all kinds of prognostic factors; (3) clinical outcomes (OS and PFS). Cox proportional hazards modeling results of hazard ratio (HR) and 95% confidence interval (CI) of prognostic factors were extracted and we applied the software Origin (version 2020; https://www.originlab.com/) to digitize and extract
When HR, 95% CI and Kaplan–Meier curves were not given directly, the data extract method was based on the method of Parmar et al. [13].

The quality of each study was assessed in accordance with the Newcastle–Ottawa Scale (NOS) [14]. As all included studies are cohort studies, the scoring was based on the following items: (1) selection: representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study; (2) comparability: comparability of cohorts on the basis of the design or analysis; (3) outcome: assessment of outcome, was follow-up long enough for outcomes to occur and adequacy of follow up of cohorts. Two reviews (YY and DJ) independently assessed the risk of bias of each trial. They cross checked the data and settled discrepancies by discussion.

**Statistical analysis**

The pooled HR and 95% CIs were calculated using Mantel–Haenszel method. A random-effects model was used
when significant heterogeneity was observed ($I^2 > 50\%$); otherwise we used a fixed-effects mode. We further performed sensitivity analysis by omitting one study at a time and examining the influence of each study on the pooled estimates of the primary outcome. In addition, we generated contour-enhanced meta-analysis funnel plots to assess potential publication bias or other biases associated with trial size. A two-sided $P$ value $< 0.05$ was considered statistically significant. The data analyses were performed using software Stata (version 15; https://www stata.com/).

**Results**

**Study selection and characteristics**

The systematic review yielded 14,107 references from five electronic databases. Eventually, we identified 82 studies with a total of 10,748 patients that met our inclusion criteria. The sample size ranged from 23 to 789 subjects. The following period ranged from 1 to 264 months. The numbers of studies comparing the OS and PFS difference between different demographic data in malignant patients with pleural effusion were 78 and 9, respectively. All 83 studies included in this systematic review were cohort studies. Figure 1 presents the PRISMA diagram of study selection. All included studies were listed in Additional file 1 (pp 3–8) and their basic characteristics were listed in Table 1.

**Quality assessment of individual studies**

The quality of each study was assessed in accordance with the Newcastle–Ottawa Scale (NOS) and was summarized in Additional file 1: eTable 2. The NOS score of all involved studies were above 6, which indicate low risk of bias.

**Included biomarkers**

To comprehensively analyze the prognostic factors of malignant patients with pleural effusion, we included all biomarkers with the number of studies more than three. The clinical parameter biomarkers of OS include age, gender, smoking status, ECOG PS, stage, histology, cytology, distant metastasis, EGFR mutation and LENT score. The clinical parameter biomarkers of PFS include age, gender, smoking status, ECOG PS, stage and EGFR mutation. In addition, many studies analyzed the serum and pleural effusion biomarkers in the prognostic value of malignant patients with pleural effusion. The serum biomarkers include white blood cell counts (WBC), NLR, hemoglobin, total protein, albumin, LDH, C-reactive protein (CRP) and vascular endothelial growth factor (VEGF). The pleural effusion biomarkers include neutrophils, PH, total protein, albumin, glucose, LDH, VEGF and survivin.

**Clinical parameter biomarkers for malignant patients with pleural effusion, primary outcome: OS**

In studies that reported the OS as outcome and evaluated the prognostic value of clinical parameter biomarkers, 36 were about the prognostic value of age, 35 of gender, 18 of smoking status, 28 of ECOG PS, 14 of stage, 17 of histology, 7 of cytology, 11 of distant metastasis, 7 of EGFR mutation and 8 of LENT score.

Figure 2a shows the forest plot of pooled HRs for the prognostic value of demographic data in OS with 95% CI. The pooled data demonstrate that elder age (HR 1.07; 95% CI 1.02–1.12), male gender (HR 1.11; 95% CI 1.05–1.17), smokers (HR 1.18; 95% CI 1.04–1.33), high ECOG PS (HR 2.35; 95% CI 1.83–3.00), M1b stage (HR 1.68; 95% CI 1.25–2.25), non-adenocarcinoma (HR 1.46; 95% CI 1.20–1.78), positive distant metastasis (HR 1.62; 95% CI 1.38–1.89) and high LENT score (HR 1.97; 95% CI 1.67–2.31) are prognostic risk factor in OS for malignant patients with pleural effusion. On the other hand, positive EGFR mutation is a protective factor in OS for malignant patients with pleural effusion (HR 0.65; 95% CI 0.56–0.74). The forest plots of each biomarker are showed on Additional file 1: eFigure 1–10. Heterogeneity testing revealed heterogeneity ($I^2$ > 50%) in age, smoking status, ECOG PS, stage and histology.

**Clinical parameter biomarkers for malignant patients with pleural effusion, secondary outcome: PFS.**

In studies that reported the PFS as outcome and evaluated the prognostic value of clinical parameters, 4 were about the prognostic value of age, 4 of gender, 5 of smoking status, 4 of ECOG PS, 4 of stage and 5 of EGFR mutation.

Figure 2b shows the forest plot of pooled HRs for the prognostic value of demographic data in PFS with 95% CI. The pooled data demonstrate that elder age (HR 1.35; 95% CI 1.04–1.74), smokers (HR 1.15; 95% CI 1.00–1.31) and M1b stage (HR 1.89; 95% CI 1.01–3.52) are prognostic risk factors in PFS for malignant patients with pleural effusion. Positive EGFR mutation is still a protective factor in PFS for lung adenocarcinoma patients with pleural effusion (HR 0.69; 95% CI 0.54–0.89). The forest plots of each biomarker are showed on Additional file 1: eFigure 11–16. Heterogeneity testing revealed heterogeneity ($I^2$ > 50%) in age, smoking status, ECOG PS and stage.

**Serum prognostic biomarkers for malignant patients with pleural effusion**

Serum prognostic biomarkers has been widely studied in the few decades and we systematically summarized these studies. In these studies, 4 were about the prognostic value of WBC, 5 of NLR, 4 of hemoglobin, 3 of total protein, 7 of albumin, 6 of LDH, 4 of CRP and 4 of VEGF.
Table 1  Baseline Characteristics of the Included Studies

| Study         | Year   | Country      | Age       | Sex              | Sample size | Follow-up (months) | Cancer type                                      | Outcome |
|---------------|--------|--------------|-----------|------------------|-------------|--------------------|--------------------------------------------------|---------|
| Sahn et al    | 1988   | USA          | 60.0±1.9  | Mixed (53.33% male) | 60          | 37                 | Mixed (not specified)                             | OS      |
| Panadero et al| 1989   | Spain        | NA        | NA               | 50          | 28                 | Pleural metastatic carcinoma                      | OS      |
| Foresti et al | 1990   | Italy        | 64.8±17.7 | Mixed (44.44% male) | 36          | 27                 | Mixed (lung, breast, mesothelioma, and others)    | OS      |
| Gottehrer et al| 1991  | USA          | NA        | NA               | 26          | 7                  | MPM                                              | OS      |
| Sugiura et al | 1997   | Japan        | 62        | Mixed (67.51% male) | 62          | 54                 | NSCLC                                            | OS      |
| Moragón et al | 1998   | Spain        | 60±13     | Mixed (45% male)   | 120         | median 9           | Mixed (NSCLC, breast, lymphoma, and others)       | OS      |
| Burrows et al | 2000   | USA          | 62(24–84) | Mixed (50% male)  | 85          | 53                 | Mixed (lung, breast, mesothelioma, and others)    | OS      |
| Heffner et al | 2000   | USA          | 61±13     | Mixed (50% male)  | 417         | 36                 | Mixed (lung, breast, unknown primary, mesothelioma, and others) | OS |
| Chen et al    | 2001   | China        | 67.9±11.2 | Mixed (71.29% male) | 202         | 49                 | Lung cancer                                      | OS      |
| Thyle’n et al | 2001   | Sweden       | NA        | Mixed (97% male)  | 100         | 100                | MPM                                              | OS      |
| Bernard et al | 2002   | France       | 65±11     | Mixed (45.71% male) | 70          | >3                 | Mixed (breast, unknown, lung, and others)         | OS      |
| Eitan et al   | 2005   | USA          | 55 (26–88)| NA               | 97          | 150                | Optimally debulked ovarian carcinoma              | PFS     |
| Aelony et al  | 2006   | USA          | NA        | Mixed (92.31% male) | 26          | 18                 | MPM                                              | OS      |
| Aoe et al     | 2006   | Japan        | 69(22–95) | Mixed (72.55% male) | 102         | 22                 | Lung cancer                                      | OS      |
| Soh et al     | 2006   | Japan        | NA        | Mixed (65.6% male) | 61          | 30                 | Lung cancer                                      | OS      |
| Bielsa et al  | 2008   | Spain        | 67±13     | Mixed (52.82% male) | 284         | 40                 | Mixed (lung, breast, unknown, and others)        | OS      |
| Wu et al      | 2008   | China        | 63.4 (37.5–85.4) | Mixed (38.97% male) | 136         | 27                 | Lung adenocarcinoma                              | OS      |
| Hsu et al     | 2009   | China        | 63(27–80) | Mixed (51.5% male) | 97          | 49                 | NSCLC                                            | OS      |
| Wu et al      | 2009   | China        | NA        | Mixed (58.33% male) | 60          | 36                 | Lung cancer                                      | OS      |
| Kotyza et al  | 2010   | Czech Republic | 63±11     | Mixed (70.73% male) | 164         | 36                 | Lung cancer                                      | OS      |
| Lan et al     | 2010   | China        | 59±16     | Mixed (55% male)   | 44          | 36                 | Mixed (lung, breast, hepatoma and others)        | OS      |
| Ozyurtkan et al| 2010  | Turkey       | 59±14     | Mixed (56% male)   | 85          | 52                 | Mixed (mesothelioma, lung, ovarian, and others)   | OS      |
| Pilling et al | 2010   | UK           | 60 (26–89)| Mixed (38.85% male) | 278         | 71                 | Mixed (breast, mesothelioma, lung, ovarian, and others) | OS      |
| Study       | Year | Country | Age             | Sex                     | Sample size | Follow-up (months) | Cancer type | Outcome         |
|------------|------|---------|-----------------|-------------------------|-------------|-------------------|-------------|-----------------|
| Tanrikulu et al | 2010 | Turkey  | NA              | Mixed (59.8% male)      | 363         | 54                | MPM         | OS              |
| Hirayama et al | 2010 | Japan   | 69.17 ± 9.64    | Mixed (82.6% male)      | 54          | 20                | MPM         | OS              |
| Park et al   | 2011 | South Korea | 68.3 ± 15.0     | Mixed (65.67% male)     | 67          | 36                | Lung cancer | OS              |
| Sakr et al   | 2011 | France  | Median 61       | Mixed (46.7% male)      | 107         | 120               | Mixed (lung, melanoma, breast, ovarian and others) | OS              |
| Yamada et al | 2011 | Japan   | 66.16 ± 10.05   | Mixed (68.9% male)      | 45          | 73                | MPM         | OS              |
| Guo et al    | 2011 | China   | 64.5 ± 9.8      | Mixed (53.13% male)     | 128         | 28                | Lung adenocarcinoma | OS              |
| Hooper et al | 2012 | UK      | 73(39–96)       | Mixed (62.14% male)     | 103         | 6                 | Mixed (mesothelioma, lung, breast, ovarian, and others) | OS              |
| Maribel et al | 2012 | Spain   | 63(53.2–80.0)   | Mixed (66.7% male)      | 30          | 40                | Lung adenocarcinoma | OS              |
| Qian et al   | 2012 | China   | NA              | Mixed (60.76% male)     | 79          | 18                | Lung adenocarcinoma | OS              |
| Qian et al   | 2012 | China   | NA              | Mixed (61% male)        | 103         | 7                 | Lung adenocarcinoma | PFS             |
| Wang et al   | 2012 | China   | NA              | Mixed (41.85% male)     | 184         | 29                | NSCLC       | OS              |
| Cheng et al  | 2013 | China   | NA              | Mixed (63.38% male)     | 71          | 60                | Lung cancer | OS              |
| Faiz et al   | 2013 | USA     | 65(17–85)       | Mixed (54.95% male)     | 111         | 172               | Acute leukemia | OS              |
| Gorgun et al | 2013 | Turkey  | 60.20 ± 13.91   | Mixed (57% male)        | 51          | 27                | Mixed (lung, breast, pancreas, and others) | OS              |
| Park et al   | 2013 | Korea   | 68.3 ± 15.0     | Mixed (66.25% male)     | 80          | 35                | Lung cancer | OS              |
| Wu et al     | 2013 | China   | 27.9–95.5       | Mixed (45.5% male)      | 448         | 81                | Lung adenocarcinoma | OS              |
| Anevavis et al | 2014 | Greece  | 69 (37–93)      | Mixed (53% male)        | 90          | 56                | Mixed (breast, mesothelioma, gastrointestinal, and others) | OS              |
| Clive et al  | 2014 | UK      | 53–80           | Mixed (53.6% male)      | 789         | 33                | Mixed (mesothelioma, hematological malignancy, gynecological malignancy, breast, and others) | OS              |
| Ni et al     | 2014 | China   | 31–81           | Mixed (47% male)        | 75          | 45                | NSCLC       | OS              |
| Xu et al     | 2014 | China   | 56.3 ± 12.5     | Mixed (46.15% male)     | 78          | 16                | Lung cancer | OS              |
| Zhang et al  | 2014 | China   | 64(36–84)       | Mixed (51% male)        | 85          | 30                | NSCLC       | OS              |
| Zhang et al  | 2014 | China   | Median 64       | Mixed (65.7% male)      | 70          | 36                | Lung cancer | OS              |
| Abrao et al  | 2015 | Brazil  | 59.6 (11.8)     | Mixed (29.07% male)     | 86          | 1                 | Mixed (lung, breast, gastrointestinal, and others) | OS              |
| Study               | Year | Country  | Age       | Sex                      | Sample size | Follow-up (months) | Cancer type                          | Outcome |
|---------------------|------|----------|-----------|--------------------------|-------------|-------------------|--------------------------------------|---------|
| Gkiozos et al       | 2015 | Greece   | NA        | Mixed (75.2% male)       | 40          | 44                | NSCLC                               | OS      |
| Porcel et al        | 2015 | Spain    | 58–78     | Mixed (77% male)         | 556         | 30                | Lung cancer                          | OS      |
| Xu et al            | 2015 | China    | 58.3±13.7 | Mixed (54.08% male)      | 98          | 100               | Lung cancer                          | OS      |
| Zamboni et al       | 2015 | Brazil   | 60.0 (1.0–95.0) | Mixed (47% male)   | 165         | 100               | Mixed (ovary, breast, lymphoma, lung, and others) | OS      |
| Zhao et al          | 2015 | China    | NA        | Mixed (48.8% male)       | 43          | 30                | Lung adenocarcinoma                  | PFS     |
| Abrao et al         | 2016 | Brazil   | 60 (24–86)| Mixed (31.25% male)      | 64          | 6                 | Mixed (lung, breast, gastrointestinal, and others) | OS      |
| Hsu et al           | 2016 | China    | Median 57 | Mixed (59% male)         | 61          | 59                | Mixed (lung, breast, and others)     | OS      |
| Kasapoglu et al     | 2016 | Turkey   | 64 (30–85)| Mixed (76% male)         | 199         | 60                | Lung cancer                          | OS      |
| Psallidas et al     | 2016 | UK       | NA        | Mixed (69.9% male)       | 75          | 28                | Mixed (not specified)                | OS      |
| Tamiya et al        | 2016 | Greece   | 68 (49–83)| Mixed (69.9% male)       | 23          | 47                | NSCLC                               | OS      |
| Terra et al         | 2016 | USA      | 58.9±12   | Mixed (28.21% male)      | 156         | 40                | Mixed (breast, lung, lymphoma, and others) | OS      |
| Usui et al          | 2016 | Japan    | NA        | Mixed (80% male)         | 25          | 50                | NSCLC                               | OS      |
| Verma et al         | 2016 | Singapore| 71 (38–92)| Mixed (51% male)         | 71          | 49                | Lung adenocarcinoma                  | OS      |
| Yang et al          | 2016 | China    | 38–75     | Mixed (48.7% male)       | 78          | 32                | Lung cancer                          | OS      |
| Amn et al           | 2017 | Indonesia| 17–85     | Mixed (44% male)         | 102         | 27                | Mixed (lung, breast, lymphoma, and others) | OS      |
| Lee et al           | 2017 | South Korea| NA        | Mixed (51.3% male)       | 158         | 72                | Lung cancer                          | OS      |
| Lu et al            | 2017 | China    | 59.3±1.56 | Mixed (65.71% male)      | 70          | 264               | NSCLC                               | OS      |
| Yang et al          | 2017 | Korea    | 71 (42–94)| Mixed (37.5% male)       | 40          | 40                | Lung adenocarcinoma                  | PFS     |
| Zheng et al         | 2017 | China    | NA        | Mixed (46.1% male)       | 128         | 55                | NSCLC                               | OS      |
| Abisheganaden et al | 2018 | Singapore| 72(38–92)| Mixed (53% male)         | 70          | 20                | Lung adenocarcinoma                  | OS      |
| Elena et al         | 2018 | Spain    | 61.6±11.2 | Mixed (56% male)         | 84          | 14                | Mixed (breast, mesothelioma, and lung cancer) | OS      |
| Han et al           | 2018 | Korea    | 70±11     | Mixed (65% male)         | 131         | 84                | Mixed (lung, breast, ovary, lymphoma, and others) | OS      |
| Jeba et al          | 2018 | India    | median 53 | Mixed (29% male)         | 48          | 70                | Mixed (lung, breast, gastrointestinal, and others) | OS      |
The pooled data of forest plot is showed in Fig. 3. The results demonstrate that high NLR (HR 2.17; 95% CI 1.22–3.88), low hemoglobin (HR 1.56; 95% CI 1.17–2.06), low total protein (HR 1.14; 95% CI 1.07–1.23), low albumin (HR 1.71; 95% CI 1.25–2.34), high LDH (HR 1.54; 95% CI 1.08–2.19), high CRP (HR 1.84; 95% CI 1.49–2.29) and high VEGF (HR 1.70; 95% CI 1.18–2.43) in serum are prognostic risk factors in OS for malignant patients with pleural effusion. In addition, serum VEGF is also a prognostic biomarker associated with a poor prognosis in OS for malignant patients. The forest plots of each biomarker in serum are showed on Additional file 1: eFigure 17–25. Heterogeneity testing revealed heterogeneity ($I^2 > 50\%$) in WBC, NLR, albumin, LDH, and VEGF for PFS.

### Pleural effusion prognostic biomarkers for malignant patients

Pleural effusion biomarkers are always the best material to test the pleural diseases. We also summarized the pleural effusion prognostic biomarkers for malignant patients. In these studies, 3 were about the prognostic value of neutrophils, 12 of PH, 10 of total protein, 4 of albumin, 12 of glucose, 14 of LDH, 10 of VEGF and 5 of survivin.

The pooled data of forest plot is showed in Fig. 4. The results demonstrate that low PH (HR 1.95; 95% CI 1.46–2.60), low glucose (HR 1.75; 95% CI 1.18–2.61), high LDH (HR 1.47; 95% CI 1.18–1.84), high VEGF (HR 1.99; 95% CI 1.67–2.37) and high survivin (HR 2.90; 95% CI 1.17–7.20) in pleural effusion are prognostic risk factors in OS for malignant patients. In addition, pleural effusion...
Fig. 2 Pooled HRs of the clinical parameters in prognostic value of OS (a) and PFS (b) in malignant patients with pleural effusion

Fig. 3 Pooled HRs of the serum biomarkers in prognostic value of OS in malignant patients with pleural effusion
VEGF is also a prognostic biomarker associated with a poor prognosis in PFS for malignant patients with pleural effusion (HR 1.42; 95% CI 1.02–2.00). The forest plots of each biomarker in serum are showed on Additional file 1: eFigure 26–34. Heterogeneity testing revealed heterogeneity ($I^2 > 50\%$) in PH, total protein, glucose, LDH, VEGF for PFS and survivin.

**Subgroup analysis**

Significant heterogeneities were observed for the prognostic significance of age ($I^2 = 58.9\%; P < 0.001$), smoking status ($I^2 = 64.7\%; P < 0.001$), ECOG PS ($I^2 = 83.5\%; P < 0.001$), stage ($I^2 = 87.5\%; P < 0.001$), histology ($I^2 = 70.4\%; P < 0.001$), serum WBC ($I^2 = 87.7\%; P < 0.001$), serum NLR ($I^2 = 87.7\%; P < 0.001$), serum albumin ($I^2 = 61.2\%; P < 0.05$), pleural effusion PH ($I^2 = 88.5\%; P < 0.001$), pleural effusion total protein ($I^2 = 81.0\%; P < 0.001$), pleural effusion glucose ($I^2 = 86.2\%; P < 0.001$), pleural effusion LDH ($I^2 = 70.5\%; P < 0.001$), pleural effusion VEGF ($I^2 = 48.7\%; P < 0.05$) and pleural effusion surviving ($I^2 = 83.3\%; P < 0.001$) for overall survival in malignant patients with pleural effusion. For progression-free survival, significant heterogeneities were observed for the prognostic significance of stage ($I^2 = 87.8\%; P < 0.001$), smoking status ($I^2 = 64.7\%; P < 0.001$), ECOG PS ($I^2 = 83.5\%; P < 0.001$), stage ($I^2 = 87.5\%; P < 0.001$), histology ($I^2 = 70.4\%; P < 0.001$), and serum VEGF ($I^2 = 80.7\%; P = 0.001$) in malignant patients with pleural effusion. Thus, subgroup analyses were performed by categorizing subgroups by cancer types. As shown in Table 1, cancer types in half of the studies were not specifically reported. In the subgroup analyses of the variables, there were no significant associations among cancer types (test for subgroup differences: $P > 0.05$) (Additional file 1: eFigure 35–41).

**Sensitivity analysis**

In order to find the source of heterogeneity, sensitivity analyses were performed in all prognostic biomarkers with $I^2 > 50\%$ (Additional file 1: eFigure 42–59). Two studies (Burrows et al [15] and Özyurtkan et al [16]) significantly influence the pooled result of pleural effusion glucose for OS in malignant patients. We have excluded these two studies for the glucose pooled result.

**Publication bias**

We analyzed all biomarkers which include more than 10 studies. The contour-enhanced meta-analysis funnel plot of HR is presented in Additional file 1: eFigure 60–71. Publication bias was present in age, stage, histology, PH of pleural and LDH in pleural effusion with the Egger tests’ p value $< 0.05$.

**Discussion**

Pleural effusion is a common clinical problem in patients with cancer, and may be due to both primary thoracic tumor or to a metastatic spread in the chest and constitutes the first sign of disease in approximately 10% of patients [17]. This study systematically summarizes all possible prognostic factors of pleural effusion caused by malignancy and may give a hint about the treatment and prognosis of malignant patients. Our main findings
indicate that except the common prognostic factors such as elder age, male gender, smoking status, more advanced disease and distant metastasis, many other indicators can be valuable prognostic factors for pleural effusion caused by malignancy. These indicators include the clinical parameters such as ECOG PS, non-adenocarcinoma histology, EGFR mutation and LENT score, the serum indicators such as NLR, hemoglobin, total protein, albumin, LDH, CRP and VEGF, and the pleural effusion indicators such as PH, glucose, LDH, VEGF and surviving.

A multi-marker strategy may be a much better approach in predicting MPE prognosis. LENT score is one of the most widely recognized scoring systems to predict survival in patients with malignant pleural effusion, calculated based on tumor type, ECOG PS, serum NLR, and pleural fluid LDH. Our study also confirms its effectiveness that LENT score shows an excellent prognostic value for malignant patients with pleural effusion, so do the LENT score calculation items (LDH, ECOG PS, NLR and tumor type). However, the LENT score has not included many important developments in the prognosis of pleural effusion [18]. In our study, positive EGFR mutation patients shows a better survival both in OS and PFS. As we know that lung adenocarcinoma with malignant pleural effusion is associated with a higher incidence of EGFR mutations [19], Abisheganaden et al. advice to modify the LENT score with EGFR mutation in lung adenocarcinoma patients [9]. The LENT score system was created as a robust prognostic score in order to aid in decision-making regarding treatment of the diverse populations of patients with malignant [7], so further modifications according to other prognostic factors may be needed to provide a better prognostic effect. The SELECT prognostication model, which included EGFR mutations, has recently been recognized as a more effective model for predicting survival in Asian MPE populations, and more studies are needed to evaluate the accuracy of this scoring system. Many biological parameters also show the prognostic value for MPE such as hemoglobin, albumin, CRP and VEGF in our study. PROMISE score combines these biological parameters and clinical parameters to accurately estimate 3-month mortality [8]. This score includes pleural fluid tissue inhibitor of metalloproteinases as one of the evaluate indexes. Unfortunately, there is not enough study of this parameter for us to analyze. Except the LENT score, modified LENT score, SELECT model and PROMISE score items, we also found that serum albumin, serum and pleural effusion VEGF, pleural effusion PH, pleural effusion glucose and pleural effusion survivin are also valuable prognostic factors for malignant patients. VEGF is a potent angiogenic regulator with a crucial role in the initiation and progression of solid malignancies [20, 21] and MPE is associated with high levels of VEGF in serum and MPE [22, 23]. According to our analysis, the increased VEGF levels in pleural fluid and serum may associated with worse OS and PFS. In addition, pleural fluid analysis has not only diagnostic but also prognostic significance in patients with malignant effusion [24]. Our results have confirmed this view. These indicators provide a new direction for the prognosis of malignant patients with pleural effusion.

Neuron-specific enolase (NSE) [25], Cancer Antigen 153 (CA153) and Cancer Antigen 125 (CA125) [26] are validated for the diagnosis and prognosis of patients with cancer. However, there is still a lack of research on whether these biomarkers in pleural effusion have prognostic values on MPE patients. The prognosis value of other combined use of markers such as Cancer ratio [27] and Cancer ratio plus [28] in predicting survival of MPE should also be studied.

Our study has some limitations. First, the combinations of some factors have significant heterogeneity. The heterogeneity may come from the different types of cancer. Second, some of the funnel plots implied possible publication bias. We have already tried to include all studies that meet the criteria, but the publication bias cannot be avoided. Third, for the outcomes, only OS and PFS were involved. Although some studies demonstrate the disease-free survival, the number is too small to summarize.

Conclusions
Our findings suggest that for malignant patients with pleural effusion, LENT score and its items are valuable prognostic biomarkers, so do the clinical parameters like stage, distant metastasis, EGFR mutation, the serum biological parameters like hemoglobin, albumin, C-reaction protein, VEGF, and the pleural effusion biological parameters like PH, glucose, VEGF and survivin.
Authors’ contributions
SHZ designed the study and have been identified as the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. PP, YY, DJ, and ZK contributed to the data collection. YY and DJ extracted the data, conducted the analysis, and produced the results figures and tables. PP and YY wrote the initial draft of the manuscript. All coauthors read and commented on the manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors declare no conflict of interest.

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