Elevated peripheral absolute monocyte count related to clinicopathological features and poor prognosis in solid tumors: Systematic review, meta-analysis, and meta-regression

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Abstract

Background: Absolute monocyte count (AMC) is often used to be assessed in cancer follow-up, which has regained interest as a potential prognostic indicator in many solid tumors, though not consistently or comprehensively. In the present study, we set out to perform a comprehensive meta-analysis of all available data regarding the prognostic significance of AMC in solid tumors. We also evaluated the association between AMC and clinical features in solid tumors.

Methods: A hazard ratio (HR) and corresponding 95% confidence interval (CI) or a p value (p) from eligible studies were extracted and subsequently pooled analyzed. Subgroup analyses and meta-regression analyses were conducted according to the confounders of included studies. In addition, the relationships between AMC and clinical characteristics were also explored in the meta-analysis.

Results: Overall, ninety-three articles comprising 104 studies with 32229 patients were finally included. The results showed that elevated AMC was associated with worse overall survival (OS) (HR = 1.615; 95% CI: 1.475-1.768; p < 0.001), disease-free survival (DFS) (HR: 1.488; 95% CI: 1.357-1.633; p < 0.001), progressive-free survival (PFS) (HR: 1.533; 95% CI: 1.342-1.751; p < 0.001) and cancer-specific survival (CSS) (HR: 1.585; 95% CI: 1.253-2.006; p < 0.001) in non-hematological tumors. Subgroup analyses according to each confounder further proved the consistent prognostic value of AMC in solid tumor outcomes. Moreover, elevated AMC was more likely to be observed in male group and patients with smoking history, and associated with longer tumor length and advanced T stage.

Abbreviations: AMC, absolute monocyte count; CCL2, C-C chemokine ligand 2; CCR2, the receptor for chemokine CCL2; CI, confidence interval; CSS, cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; MCP-1, monocyte chemoattractant protein-1; MDSC, myeloid-derived suppressor cell; NK cell, natural killer cell; NOS, Newcastle–Otawa Quality Assessment Scale; OR, odds ratio; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progressive-free survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta- Analyses guidelines; RFS, recurrence-free survival; ROC, receiver operating characteristic curve; SAR, survival after recurrence; SMD, standardized mean difference; TAM, tumor-associated macrophage; TME, tumor microenvironment; VEGF, vascular endothelial growth factor.

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Cancer remains one of the leading causes of death and a major health care challenge worldwide.¹ The prominent differences of cancer profiles in individual countries are associated with marked geographic diversity.¹ Despite substantial progress, cancer morbidity and mortality rates have been rapidly growing in both developing and developed countries.¹ Based on the statistics, 1806,590 new cancer cases and 606,520 cancer deaths are projected to occur in the United States in 2020.² Similarly, the Chinese national cancer registries reported about 3929,000 new cancer cases and 2338,000 cancer deaths in China in 2015.³

In the last decade, there have been the paradigms of chemotherapy being transformed from empiric therapy to individual pharmacogenomics- and genetics-based personalized medicine, coinciding with rapid technological advances and brilliant discoveries in many fields such as genetics and molecular biomarkers.⁴ These markers have been recognized to reflect the characteristics of cancer signatures, optimize therapy decisions and provide timeliness information about the response to personalized treatment.⁵ While several biomarkers specific to particular cancer types have been applied routinely, such as PSA for prostate cancer, general decisive biomarkers used for overall cancers are unavailable.⁵ Thus, the identification of new potential tumor biomarkers with improved test convenience and sensitivity carries great significance to provide quicker diagnosis and more accurate prognosis.

With the increased understanding of tumor immunology, the dual interaction between cancer and the immune system has been recognized and the microenvironment in which the cancer cells grow has been highlighted.⁶-⁸ For a broad point of view, tumor microenvironment (TME) is a highly complicated heterogeneous ecosystem containing not only tumor cells, but also a variety of non-immune and immune cells.⁹ The immune contexture describes the density, function orientation, and spatial organization of the immune cell populations, including innate immune cells (e.g., macrophage, neutrophils, or natural killer cell (NK cell)), adaptive immune cells (e.g., T and B lymphocytes), and myeloid and lymphoid lineages.⁹ Immune cells play a pivotal role in the cytokine- and chemokine-mediated imbalanced immune response, which attributes to their inherent functions and the molecules they express.¹⁰ These cells have been reported to participate in the manifestation of tumor recognition and the consecutive steps of malignancy initiation, progression, and metastasis.¹¹,¹² In addition, previous study indicated that tumor cells may modify the immunophenotype of immune cells and extracellular microenvironment, thus enhancing the deterioration of the immune contexture which determines tumor outcomes.¹³ The quantitative assessment of immunological status based on immune cells was applied in the prediction of some solid tumors.¹⁴

Tumor-associated macrophages (TAMs), derived from the infiltrating bone marrow-derived monocytes, are a major component in TME and therefore were considered as conspicuous stromal targets in many types of solid tumors.⁶,⁷ Tumor-associated macrophages could differentiate into “proinflammatory” M1 phenotypes with antitumor activity or “proangiogenic and immunosuppressive” M2 phenotypes according to the microenvironment. The dominant phenotype M2 was thought to be important in tumor progression, angiogenesis, and immune tolerance through promoting fibroblast proliferation, extracellular matrix deposition, and immunosuppression in the late stages.¹⁵-¹⁷ Recently, the rapid development of biotechnologies has boosted the understanding of the interplay between cancer cells and monocytes/macrophages.¹⁸ It is suggested that monocyte subpopulation distribution and transcriptomes are significantly perturbed by cancer, subsequently reflecting patients outcomes.¹⁸ In mouse models of cancer, monocytes have been shown to contribute to tumor progression, metastasis, and anti-vascular endothelial growth factor therapy resistance.¹⁹,²⁰ Monocytes have been shown to be associated with cancer prognosis in patients with subdividing cancers, such as follicular lymphoma and colorectal cancer, although this line of research is still subject to debate.²¹,²² Some data showed an insignificant prognostic value of monocytes in cervical cancer or malignant pleural mesothelioma.²³,²⁴ Much more attention was paid to hematological tumors and lymphocyte-to-monocyte ratio.²⁵,²⁶ Hence, the present researches available on the association between absolute monocyte count (AMC) and solid tumors have not been systematically analyzed so far, and evidence for the use of the peripheral AMC as a predictor of clinical outcome in solid tumors remained controversial.

Therefore, we performed a meta-analysis with in order to validate the role of monocyte as a predictor in solid tumors. In addition, we also integrated data to demonstrate the relevant clinicopathological factors in relation to peripheral
monocyte count, which is of the essence to tailor the personalized cancer treatment strategy.

2 | METHODS

2.1 | Data sources and search strategy

The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). An electronic literature search was conducted in the databases of Medline (PubMed), Embase, and the Web of Science on April 14, 2020, by two investigators independently, with the following search terms: “absolute monocyte count,” “monocyte count,” “cancer,” “carcinoma,” and “neoplasm.” In addition, manual searches were supplemented in all citation lists of the retrieved articles for further investigation of potentially relevant studies. Language was restricted to English and Chinese.

2.2 | Criteria for inclusion and exclusion

Studies included in this meta-analysis meet the following criteria: (1) patients with solid tumors were studied; (2) the prognostic impact of AMC on overall survival (OS), cancer-specific survival (CSS), progressive-free survival (PFS), disease-free survival (DFS) and/or recurrence-free survival (RFS) was evaluated; (3) a hazard ratio (HR) with 95% confidence interval (CI) could be extracted in univariate or multivariate analysis of Cox hazard model, or could be estimated by Parmar’s method; (4) AMC was calculated as a dichotomized variable by a cut-off value. Studies were excluded if they match any of the following: (1) reference abstracts, case reports, conference abstracts, reviews or meta-analysis; (2) studies on hematological malignancies; (3) insufficient data for estimating HR and 95% CI; (4) studies reporting AMC only as a continuous variable; (5) duplicate publications or repeated analysis. Moreover, if studies with overlapping patients were identified, the study with the most information and most recent publication was included. The full-texts of the relevant articles were retrieved to assess eligibility.

2.3 | Data extraction and quality assessment

Two investigators performed data extraction independently with a standard extraction form. The following data were extracted: first author’s surname, publication year, country, region, patient sources, cancer type, study design, characteristics of cancer (distant metastasis, TNM stage, treatment), characteristics of the study cohort (sample size, mean age, gender), testing time of monocyte, cut-off value defining low monocyte, method for the selection of cut-off value, outcome measures (OS, DFS, CSS, RFS, PFS assessed as HRs and corresponding 95% CI and/or p values) model of survival analysis (multivariate or univariate).

The reviewers independently assessed the methodological quality of the included studies by the Newcastle–Ottawa Quality Assessment Scale (NOS). The 9-point scoring system comprised three domains of quality including selection, comparability, and outcome assessment, and studies with NOS scores of more than six were defined as high-quality studies. Any discrepancies between reviewers were resolved by discussion until a consensus was reached.

2.4 | Statistical analysis

This meta-analysis was performed with STATA version 14.0 (STATA Corporation, College Station, TX, USA). The survival data were measured by HR and 95% CI. The aggregated HRs and 95% CIs, either directly extracted or presented in the form of Kaplan-Meier survival curves, were calculated to evaluate the prognostic value of AMC on the long-term prognosis (OS/DFS/PFS/CSS) using low AMC group as a reference. The relationships between the AMC and certain clinical features of patients were also assessed with STATA version 14.0. Odds ratios (ORs) for dichotomous variables and standardized mean differences (SMDs) for continuous variables with their 95% CIs were regarded as summarized statistics, respectively. Statistical significance was indicated when \( p < 0.05 \) in data synthesis. Besides, we used the outcomes in multivariate analysis whenever the univariate and multivariate analyses were available. The heterogeneity of pooled studies was measured by Cochran’s Q test and Higgins I-squared (\( I^2 \)) statistic; \( p < 0.1 \) or \( I^2 > 50\% \) was defined as significant heterogeneity. The random-effects model was used in the analysis. Subgroup analysis was performed based on region, sample size, cut-off value, cancer type, distant metastatic status, TNM stage, testing time of blood, analysis method, and study quality to explore the heterogeneity sources. Then, meta-regression analyses were conducted to determine the hazard effects of covariates. Publication bias was evaluated by Begg’s and Egger’s test. Sensitivity analysis was conducted to explore the influence on the pooled effect size after removing a single study each time. Two-sided \( p < 0.05 \) was considered statistically significant.

3 | RESULTS

3.1 | Studies characteristics

The initial literature search identified a total of 6016 potentially relevant publications. After thoroughly screening
the titles and abstracts by two investigators independently, the full-texts of 173 potential studies were selected for further identification. Finally, 102 retrospective studies and 2 retrospective-prospective studies from 93 eligible papers that met the inclusion criteria were included in this meta-analysis.22–24,30–119 The flow diagram of the selection procedure is presented in Figure 1.

Of those 104 studies, 82 were based on Asians and 22 on non-Asians. According to the types of cancer, 41 studies were on abdominal cancers, 30 studies on thoracic cancers, 14 studies on pelvic cancers, 12 studies on head and neck cancers, 6 studies on melanoma, and 1 study remained unknown. Based on the testing time of blood, majority of the included studies were pre-treatment (n = 59) and pre-operative (n = 42), while one study was post-treatment and two studies remained unknown. There were 65 studies estimated as high-quality studies and 39 low-quality studies. The endpoints OS, DFS, CSS PFS, and survival after recurrence (SAR) were addressed in 88, 41, 23, 10, and 1 studies, respectively. As shown in Table 1, the receiver operating characteristic curves (ROC) were applied to detect the optimal cut-off values in 40 studies with low cut-off value, studies with multivariate analysis, and low-quality studies with decreased heterogeneity. Similar associations were seen in analyses stratified by TNM stage and distant metastatic status, as well as in pre-treatment and pre-operative studies. Considering various cancer types may lead to inconsistent results, a subgroup analysis according to cancer type was conducted. Most subgroups showed a negative prognostic effect of elevated AMC. This includes the subgroups of breast cancer, cervical cancer, colorectal cancer, esophageal cancer, hepatocellular cancer, head and neck cancer, lung cancer, melanoma, pancreatic cancer, and prostate cancer. Of subgroups stratified by cancer type, the highest effect on OS was found in cervical cancer (HR: 2.917; 95% CI: 1.186-7.175; p = 0.020) and no heterogeneity was found in the prostate cancer subgroup (HR: 2.253; 95% CI: 1.665-3.048; p < 0.001) (Figure 3). When stratified by primary tumor sites, the pooled highest effect on OS was found in pelvic cancers (HR:2.111, 95% CI: 1.480-3.011, p < 0.001). (Table 2). Meta-regression analyses were performed, while none of an individual parameter was identified as the cause of heterogeneity (Table 2).

3.2 | Overall survival

A total of 88 studies including 29,130 patients provided suitable data for OS analysis. Comparing with low monocyte count, the elevated AMC showed a significant relevance with poorer survival (HR = 1.615; 95% CI: 1.475-1.768; p < 0.001) (Figure 2). The test of heterogeneity was significant and random-effects model was used (I² = 83.50%; p < 0.001). Subgroup analyses were performed based on the available data. The subgroup analyses revealed a significant association between higher AMC and unfavorable cancer prognosis in Asian patients, studies with large sample size, studies with low cut-off value, studies with multivariate analysis, and low-quality studies with decreased heterogeneity. Similar associations were seen in analyses stratified by TNM stage and distant metastatic status, as well as in pre-treatment and pre-operative studies. Considering various cancer types may lead to inconsistent results, a subgroup analysis according to cancer type was conducted. Most subgroups showed a negative prognostic effect of elevated AMC. This includes the subgroups of breast cancer, cervical cancer, colorectal cancer, esophageal cancer, hepatocellular cancer, head and neck cancer, lung cancer, melanoma, pancreatic cancer, and prostate cancer. Of subgroups stratified by cancer type, the highest effect on OS was found in cervical cancer (HR: 2.917; 95% CI: 1.186-7.175; p = 0.020) and no heterogeneity was found in the prostate cancer subgroup (HR: 2.253; 95% CI: 1.665-3.048; p < 0.001) (Figure 3). When stratified by primary tumor sites, the pooled highest effect on OS was found in pelvic cancers (HR:2.111, 95% CI: 1.480-3.011, p < 0.001). (Table 2). Meta-regression analyses were performed, while none of an individual parameter was identified as the cause of heterogeneity (Table 2).

3.3 | Disease-free survival

There were 41 studies, comprising 11,514 patients, reporting HRs for DFS. Overall, high AMC was significantly associated with worse DFS (HR:1.488; 95% CI: 1.357-1.633; p < 0.001) (Figure 4). Low heterogeneity was shown between these studies (I² = 32.00%; p = 0.028). The analyses demonstrated that elevated AMC was positively related to pooled HR for DFS when stratified by region, sample size, cut-off value, analysis method, and study quality. In subgroup analyses according to cancer type, studies on breast
TABLE 1  The baseline characteristics of included studies

| Author, year | Region | Cancer type | Distant metastasis | TMN stage | Test time | N^a | Mean age | Cut-off value (/mm^3) | Method^c | Endpoint | Analysis | NOS score |
|--------------|--------|-------------|-------------------|-----------|-----------|-----|---------|----------------------|----------|----------|----------|-----------|
| **Head and neck cancers** | | | | | | | | | | | | |
| Bobdey, 2017 | Asian | Oral cavity cancer | Both | I-IV | Pre-treatment | 471 | 50 | 500 | ROC | OS | MV | 8 |
| Chen, 2017 | Asian | HNC | Both | I-IV | Pre-treatment | 270 | 56.5^b | 1000 | Previous study | OS | MV | 7 |
| Fujikawa, 2019 | Asian | Tongue cancer | NA | I-IV | Pre-operative | 103 | 63^b | 320 | Mean value | OS | MV | 7 |
| Jiang, 2015 | Asian | NPC | Yes | IV | Pre-treatment | 672 | 46 | 665 | ROC | OS | MV | 5 |
| Li, 2013 | Asian | NPC | No | I-IV | Pre-treatment | 1547 | 51 | 475 | ROC | OS/DFS | MV/MV | 6 |
| Lin, 2014 | Asian | NPC | Yes | IV | Pre-treatment | 256 | 53.6 | 350 | ROC | OS | MV | 6 |
| Huang, 2015 (1) | Non-Asian | OPC | NA | I-IV | Pre-treatment | 510 | 57.5 | 600 | Median value | OS/RFS | UV/UV | 8 |
| Huang, 2015 (2) | Non-Asian | OPC | NA | I-IV | Pre-treatment | 192 | 65 | 700 | Median value | OS/RFS | UV/UV | 8 |
| Takahashi, 2019 | Asian | OPC | Both | I-IV | Pre-treatment | 75 | 65^b | 485 | ROC | OS/PFS | MV/MV | 6 |
| Tsia, 2014 | Asian | Oral cavity cancer | Both | I-IV | Pre-treatment | 202 | 53 | 403 | Median value | CSS | MV | 8 |
| Yang, 2018 | Asian | HPC | No | I-IV | Pre-treatment | 197 | NA | 630 | P value^a | OS/DFS/CSS | UV/UV/UV | 7 |
| Yokato, 2020 | Asian | Thyroid cancer | No | I-IVA | Pre-operative | 570 | 58^b | 260 | ROC | RFS | UV | 6 |
| **Thoracic cancers** | | | | | | | | | | | | |
| Botta, 2013 (1) | Asian | Lung cancer | Both | III-IV | Pre-treatment | 73 | 58.57 | 600 | ULN | PFS | UV | 7 |
| Botta, 2013 (2) | Non-Asian | Lung cancer | Both | III-IV | Pre-treatment | 39 | 67.85 | 600 | ULN | PFS | UV | 7 |
| Charrier, 2019 | Non-Asian | Lung cancer | Both | III-IV | Pre-treatment | 148 | 62^b | 800 | NA | OS/PFS | MV/MV | 8 |
| Chen, 2020 | Asian | Breast cancer | No | II-III | Pre-treatment | 262 | 48^b | 340 | ROC | OS/DFS | UV/UV | 7 |
| Go, 2015 | Asian | Lung cancer | Both | I-IV | Pre-treatment | 134 | 68.5 | 640 | Median value | OS | MV | 6 |
| Hai, 2018 | Asian | Lung cancer | No | I-IIIA | Pre-operative | 433 | 60.6 | 375 | ROC | OS/DFS | UV/UV | 9 |
| Han, 2016 | Asian | ESCC | No | I-III | Pre-operative | 218 | 60.5 | 420 | ROC | OS/DFS | MV/MV | 9 |
| Huang, 2015 | Asian | ESCC | No | NA | Pre-operative | 348 | 59.2 | 550 | ROC | CSS | MV | 7 |
| Huang, 2019 (1) | Asian | Breast cancer | Both | I-IV | Pre-treatment | 133 | NA | 440 | NA | OS/DFS | UV/UV | 7 |
| Huang, 2019 (2) | Asian | Breast cancer | Both | I-IV | Pre-treatment | 317 | NA | 440 | NA | OS/DFS | UV/UV | 7 |
| Huang, 2019 (3) | Asian | Breast cancer | Both | I-IV | Pre-treatment | 57 | NA | 440 | NA | OS/DFS | UV/UV | 7 |
| Huang, 2019 (4) | Asian | Breast cancer | No | I-III | Pre-treatment | 94 | NA | 440 | NA | OS/DFS | UV/UV | 7 |
| Kumagai, 2014 | Asian | Lung cancer | No | I-III | Pre-operative | 302 | 67 | 430 | ROC | OS/RFS | MV/MV | 8 |
| Lee, 2017 | Asian | Lung cancer | Both | III-IV | Pre-treatment | 135 | NA | 800 | Previous study | OS | MV | 7 |

(Continues)
| Author, year | Region | Cancer type | Distant metastasis | TMN stage | Test time | N | Mean age | Cut-off value (mm) | Method | Endpoint | Analysis | NOS score |
|--------------|--------|-------------|--------------------|-----------|-----------|---|----------|------------------|--------|-----------|----------|-----------|
| Lee, 2018(1) | Asian  | Breast cancer| No                 | I-III     | Pre-operative | NA | NA       | 360               | Median value | DFS      | UV       | 7        |
| Lee, 2018(2) | Asian  | Breast cancer| No                 | I-III     | Pre-operative | NA | NA       | 360               | Median value | DFS      | UV       | 7        |
| Lin, 2014    | Asian  | Lung cancer  | Both               | III-IV    | Pre-treatment | 370 | 63.6     | 450               | ROC     | OS/PFS   | MV/MV    | 6        |
| Ni, 2014     | Asian  | Breast cancer| No                 | I-III     | Pre-treatment | 542 | 49       | 400               | Mean value | DFS      | MV       | 7        |
| Sakin, 2019  | Asian  | Lung cancer  | Yes                | IV        | Pre-treatment | 113 | 65       | 860               | Normal value | OS       | UV       | 6        |
| Schernberg, 2017 | Non-Asian | ESCC  | No                 | I-III     | Pre-treatment | 126 | 62       | 1000              | NA      | OS/PFS   | UV/MV    | 7        |
| Song, 2019   | Asian  | ESCC        | No                 | I-III     | Pre-operative | 686 | 61       | 500               | Median value | OS/DFS   | MV/UV    | 7        |
| Soyano, 2018 | Non-Asian | Lung cancer | Both              | NA       | Pre-treatment | 157 | 66       | 630               | P value** | OS/PFS   | MV/MV    | 7        |
| Tang, 2016   | Asian  | Lung cancer  | No                 | III       | Pre-treatment | 78  | 57       | 600               | Previous study | OS       | UV       | 5        |
| Tanizaki, 2018| Asian  | Lung cancer  | Both               | III-IV    | Pre-treatment | 134 | 68       | 650               | Previous study | OS/PFS   | UV/UV    | 7        |
| Tanrikulu, 2016 | Non-Asian | MPM   | Both               | I-IV      | Pre-treatment | 292 | 58.4     | 550               | ROC     | OS       | MV       | 6        |
| Wang, 2019   | Asian  | ESCC        | Both               | I-IV      | Pre-treatment | 43  | 62       | 330               | NA      | OS       | MV       | 6        |
| Wen, 2015    | Asian  | Breast cancer| No                 | I-III     | Pre-operative | 2000| 49.4     | 480               | ROC     | OS       | MV       | 8        |
| Zhang, 2017  | Asian  | MPM         | NA                 | NA       | Pre-treatment | 105 | 56       | 545               | ROC     | OS       | MV       | 8        |
| Zhu, 2017    | Asian  | ESCC        | No                 | IIB       | Pre-operative | 220 | NA       | 630               | Previous study | OS/DFS   | UV/UV    | 9        |

**Abdominal cancers**

| Author, year | Region | Cancer type | Distant metastasis | TMN stage | Test time | N | Mean age | Cut-off value (mm) | Method | Endpoint | Analysis | NOS score |
|--------------|--------|-------------|--------------------|-----------|-----------|---|----------|------------------|--------|-----------|----------|-----------|
| Abu-Shawer, 2019 | Asian  | Gastric cancer | Both              | I-IV      | Pre-treatment | 502 | 54       | 660               | Median value | OS       | UV       | 6        |
| Cong, 2016    | Asian  | Gastric cancer| No                 | II-III    | Pre-operative | 188 | 77       | 350               | ROC     | OS       | MV       | 7        |
| Feng, 2018    | Asian  | Gastric cancer| No                 | I-III     | Pre-operative | 3243| 58       | 510               | X-tile  | OS       | MV       | 6        |
| Fuj iwara, 2019| Asian  | DEBDC       | Both               | I-IV      | Pre-operative | 121 | 66.7     | 300               | ROC     | OS/DFS   | UV/UV    | 8        |
| Giacomelli, 2017| Non-Asian | Pancreatic cancer | No                | I-III     | Pre-treatment | 57  | 62       | 800               | NA      | PFS      | UV       | 6        |
| Gu, 2019      | Asian  | HCC         | No                 | I-III     | Pre-treatment | 116 | 51       | 400               | Median value | OS/RFS   | UV/UV    | 7        |
| Haruki, 2017  | Asian  | Colorectal cancer | Yes              | IV        | Pre-operative | 89  | 64       | 300               | Mean value | OS/DFS   | UV/UV    | 7        |
| Hu, 2016      | Asian  | Colorectal cancer | Both             | I-IV      | Pre-operative | 210 | 56.1     | 505               | ROC     | OS       | MV       | 7        |
| Inamoto, 2019 | Asian  | Colorectal cancer | Both             | I-IV      | Pre-operative | 448 | 69       | 400               | ROC     | OS/DFS/CSS| MV/MV/ MV| 6        |
| Ishihara, 2019| Asian  | Renal cell cancer | Yes              | IV        | Pre-operative | 58  | NA       | 650               | Previous study | OS/PFS   | UV/UV    | 7        |
| Author, year  | Region   | Cancer type          | Distant metastasis | TMN stage | Test time     | N<sup>a</sup> | Mean age | Cut-off value (/mm)<sup>b</sup> | Method<sup>c</sup> | Endpoint | Analysis | NOS score |
|--------------|----------|----------------------|--------------------|-----------|---------------|--------------|-----------|-------------------------------|-------------------|----------|----------|-----------|
| Iwase, 2013  | Asian    | Gallbladder cancer   | No                 | NA        | Post-operative| 34           | 67        | 300                           | Previous study    | OS/DFS   | UV/UV    | 7         |
| Kim, 2014    | Asian    | HCC                  | No                 | NA        | Pre-operative | 256         | 54        | 300                           | ROC               | RFS      | UV       | 8         |
| Krakowska, 2018 | Non-Asian | Colorectal cancer | Both               | III-IV    | Pre-treatment | 295         | 63        | NA                            | Normal value      | OS/PFS   | UV/UV    | 7         |
| Lee, 2016    | Asian    | Colorectal cancer    | Yes                | IV        | Pre-treatment | 120         | NA        | 413.3                         | ROC               | OS       | UV       | 6         |
| Leith, 2007<sup>(1)</sup> | Non-Asian | Colorectal cancer | No                 | I-III     | NA            | 149         | NA        | 900                           | Previous study    | OS/CSS   | UV/UV    | 6         |
| Leith, 2007<sup>(2)</sup> | Non-Asian | Colorectal cancer | Yes                | IV        | NA            | 84          | NA        | 900                           | Previous study    | CSS      | UV       | 6         |
| Li, 2016     | Asian    | Pancreatic cancer    | No                 | I-III     | Pre-operative | 144         | 62        | 400                           | ROC               | OS/RFS   | UV/UV    | 6         |
| Li, 2018     | Asian    | Colon cancer         | No                 | I-III     | Pre-operative | 216         | 64        | 350                           | Mean value        | OS/PFS   | MV/MV    | 7         |
| Lin, 2014    | Asian    | HCC                  | Both               | I-IV      | Pre-treatment | 216         | 64.8      | 380                           | ROC               | OS       | MV       | 9         |
| Lin, 2016    | Asian    | Colorectal cancer    | Yes                | IV        | Pre-treatment | 488         | 54        | 550                           | ROC               | OS/PFS   | MV/MV    | 6         |
| Neal, 2015   | Non-Asian| Colorectal cancer    | Yes                | IV        | Pre-operative | 302         | 64.8      | 700                           | ROC               | OS/CSS   | UV/UV    | 7         |
| Oh, 2016     | Asian    | Colorectal cancer    | No                 | II        | Pre-operative | 261         | 65        | 520                           | ROC               | OS/DFS   | UV/UV    | 7         |
| Paik, 2014   | Asian    | Colorectal cancer    | Both               | I-IV      | Pre-operative | 600         | 62.3       | 900                           | ROC               | OS/DFS   | MV/MV    | 6         |
| Pan, 2018    | Asian    | Gastric cancer       | No                 | I-III     | Pre-operative | 870         | 60<sup>b</sup> | 230                          | ROC               | OS       | UV       | 7         |
| Qi, 2015<sup>(1)</sup> | Asian | Pancreatic cancer | Both               | III-IV    | Pre-treatment | 211         | 61.2       | 400                           | Median value      | OS       | MV       | 5         |
| Qi, 2015<sup>(2)</sup> | Asian | Pancreatic cancer | Both               | III-IV    | Pre-treatment | 110         | 60.8       | 400                           | Median value      | OS       | UV       | 5         |
| Ren, 2016    | Asian    | HCC                  | No                 | NA        | Pre-operative | 101         | 49.2       | 456                           | ROC               | OS/DFS   | UV/UV    | 8         |
| Saito, 2019  | Asian    | Gastric cancer       | No                 | I-III     | Pre-operative | 445         | NA        | 658.5                         | ROC               | OS       | UV       | 6         |
| Sasaki, 2006 | Asian    | HCC                  | NA                 | NA        | Pre-operative | 198         | 63        | 300                           | Median value      | DFS/CSS  | MV/MV    | 9         |
| Sasaki, 2007 | Asian    | Colorectal cancer    | Yes                | IV        | Pre-operative | 97          | 62.6       | 300                           | Median value      | CSS      | MV       | 9         |

(Continues)
| Author, year | Region | Cancer type | Distant metastasis | TMN stage | Test time | N^a | Mean age | Cut-off value (μm^3) | Method^g | Endpoint | Analysis | NOS score |
|-------------|--------|-------------|-------------------|-----------|-----------|-----|---------|----------------------|-----------|----------|----------|-----------|
| Shen, 2014  | Asian  | HCC         | No                | NA        | Pre-operative | 351 | 50.1    | 545                  | ROC       | OS/DFS   | MV/MV    | 8         |
| Shibutani, 2017 | Asian | Colorectal cancer | No | I-III | Pre-operative | 189 | 68     | 300                  | Previous studies | OS/RFS | UV/UV    | 6         |
| Tanio, 2019  | Asian  | Colorectal cancer | Both | I-IV | Pre-operative | 361 | NA     | 421.5                | ROC       | OS       | UV       | 7         |
| Urakawa, 2019 | Asian | Gastric cancer | No | II-III | Pre-operative | 278 | 68^b    | 401                  | Median value | OS/RFS | MV/MV    | 8         |
| Wang, 2018   | Asian  | Gastric cancer | No | I-III | Pre-treatment | 104 | 60     | 330                  | Median value | OS       | UV       | 8         |
| Wang, 2019   | Asian  | Gastric cancer | No | III   | Pre-operative | 182 | 55.7   | 440                  | Median value | OS/DFS | UV/UV    | 7         |
| Wu, 2019     | Asian  | Colorectal cancer | No | I-III | Pre-treatment | 153 | 56^b   | 330                  | Median value | OS       | UV       | 8         |
| Yamamoto, 2020 | Asian | Colorectal cancer | No | I-III | Pre-operative | 463 | NA     | 455.5                | ROC       | OS       | UV       | 6         |
| Yang, 2017   | Asian  | Colon cancer | Yes | IV    | Pre-treatment | 95  | 56     | 370                  | Median value | OS/PFS  | MV/MV    | 7         |
| Zhang, 2015  | Asian  | Rectal cancer | No | IIIB  | Pre-operative | 270 | NA     | 595                  | ROC       | OS/DFS  | MV/MV    | 8         |
| Zhang, 2016  | Asian  | ICC         | Both | NA   | Pre-treatment | 187 | 60^b   | 500                  | Median value | OS       | MV       | 6         |
| Pelvic cancers |
| Abu-Shawer, 2019 | Asian | GNC      | Both | III-IV | Pre-treatment | 259 | 57     | 590                  | ROC       | OS/EFS  | UV       | 6         |
| Burgess, 2020 | Non-Asian | Endometrial cancer | Both | I-IV  | Pre-operative | 310 | 63.8   | 700^e                | Previous study | OS/DFS/PFS | MV/MV/UV | 7         |
| Eo, 2018     | Asian  | Cervical cancer | No  | I-II  | Pre-treatment | 233 | 51^b   | 800                  | Previous study | OS/PFS  | MV/MV    | 8         |
| Hayashi, 2017 | Asian | Prostate cancer | No | I-III | Pre-operative | 248 | 66     | 369                  | Median value | RFS      | MV       | 6         |
| Ittiamornlert, 2019 | Asian | Cervical cancer | Both | I-IV  | Pre-treatment | 355 | 52.5   | 970                  | NA        | OS/PFS  | UV/UV    | 6         |
| Lee, 2012    | Asian  | Cervical cancer | No  | I-IVA | Pre-treatment | 788 | 51     | 349                  | Median value | OS/PFS  | MV/MV    | 6         |
| Lee, 2020    | Asian  | Cervical cancer | No  | II-III | Pre-treatment | 125 | 53.67  | 330                  | ROC       | OS/DFS  | UV/UV    | 6         |
| Li, 2016     | Asian  | Cervical cancer | No  | II-IVA | Pre-treatment | 424 | 47     | 380                  | ROC       | OS/PFS  | MV/MV    | 6         |
| Machida, 2017 | Non-Asian | Endometrial cancer | Both | I-IV  | Pre-treatment | 141 | 58.2   | 400                  | NA        | SAR     | UV       | 8         |

(Continues)
| Author, year | Region | Cancer type | Distant metastasis | TMN stage | Test time | N<sup>a</sup> | Mean age | Cut-off value (/mm<sup>3</sup>) | Method<sup>e</sup> | Endpoint | Analysis | NOS score |
|-------------|--------|-------------|-------------------|------------|-----------|-------------|----------|-------------------|----------------|-----------|----------|----------|
| Matsuo, 2015 | Non-Asian | Endometrial cancer | NA | I-IV | Pre-operative | 541 | 52.1 | 700 | P value*** | OS/DFS | MV/MV | 8 |
| Shigeta, 2016<sup>(1)</sup> | Asian | Prostate cancer | Yes | IV | Pre-treatment | 106 | 73 | 400 | ROC | OS/PFS | MV/MV | 6 |
| Shigeta, 2016<sup>(2)</sup> | Asian | Prostate cancer | Yes | IV | Pre-treatment | 108 | 71 | 400 | ROC | OS/PFS | MV/MV | 6 |
| Singh, 2017 | Non-Asian | Cervical cancer | No | I-IVA | Pre-treatment | 181 | 52 | 660 | Median value | OS/PFS | UV/UV | 8 |
| Wang, 2017 | Asian | Prostate cancer | Both | I-IV | Pre-treatment | 290 | 75 | 425 | ROC | OS/PFS/CSS | MV/UV/ MV | 8 |
| Other cancers | | | | | | | | | | | | |
| Gandini, 2016 | Non-Asian | Melanoma | Yes | IV | Pre-treatment | 127 | 55 | 460 | ULN | OS | MV | 7 |
| Martens, 2016 | Non-Asian | Melanoma | Yes | IV | Pre-treatment | 209<sup>c</sup> | 58 | 413.3 | P value* | OS | UV | 6 |
| Rochet, 2015<sup>(1)</sup> | Non-Asian | Melanoma | No | III | Pre-operative | 153 | 59<sup>b</sup> | 600 | P value**** | OS/RFS | MV/MV | 6 |
| Rochet, 2015<sup>(2)</sup> | Non-Asian | Melanoma | Yes | IV | Pre-operative | 74 | 56<sup>b</sup> | 600 | P value**** | OS/RFS | MV/MV | 6 |
| Schmidt, 2005 | Non-Asian | Melanoma | Yes | IV | Pre-treatment | 321 | 51 | NA | Normal value | OS | UV | 5 |
| Shi, 2020 | Asian | Malignant cancers<sup>d</sup> | Both | NA | Pre-treatment | 193 | 65<sup>b</sup> | 370 | P value*** | OS | MV | 7 |
| Wagner, 2020 | Non-Asian | Melanoma | No | I-II | Pre-operative | 1412<sup>c</sup> | 63 | 810 | P value*** | OS | MV | 7 |

NOS: Newcastle-Ottawa Quality Assessment Scale; OS: overall survival; DFS: disease-free survival; PFS: progression-free survival; SAR: survival after the recurrence of cancer; MV: multivariate analysis; UV: univariate analysis; ULN: upper limit of normal; DEBDC: distal extrahepatic bile duct cancer; ESCC: esophageal squamous cell carcinoma; GNC: Gynecological cancers; HCC: hepatocellular carcinoma; HPC: hypopharyngeal squamous cell carcinoma; ICC: intrahepatic cholangiocarcinoma; MPE: malignant pleural effusion; MPM: malignant pleural mesothelioma; NPC: nasopharyngeal carcinoma; OPC: oropharyngeal cancer; TET: thymic epithelial tumor; ROC: receiver operating characteristic curve; NA: not available information.

<sup>a</sup>Number of included patients.

<sup>b</sup>Median.

<sup>c</sup>Existing missing data.

<sup>d</sup>Malignant cancers with pleural effusion.

<sup>e</sup>Method of determining cut-off value.

*<sup>p</sup> value: the lowest significant log-rank <sup>p</sup>-value of all analyzed eccentric cut-off points.

**<sup>p</sup> value: the cut-off value was assessed by Contal and O'Quigley.

***<sup>p</sup> value: the cut-off value to maximize the survival outcome for DFS and OS.

****<sup>p</sup> value: the significant value of <sup>χ</sup><sup>2</sup> test of the log-rank test analysis for different cut-off points between the 25% and 75% quartile values.
cancer, endometrial cancer, esophageal cancer, lung cancer, and melanoma also demonstrated the negative effect of high AMC on outcomes with consistency. In addition, we found poor DFS in studies with IV stage cancers, but the estimate was insignificant (HR: 1.279; 95% CI: 0.855-1.914; $p = 0.231$) (Table 2).

### 3.4 Progressive-free survival

Data on the association between AMC and PFS were derived from 23 studies involving 5,126 patients. Overall higher AMC associated with worse prognosis (HR: 1.533; 95% CI: 1.342-1.751; $p < 0.001$), with moderate heterogeneity ($I^2 = 45.50%$; $p = 0.010$) (Table 2, Figure 4). Exploratory subgroup analyses were performed according to region, cancer type and TNM stages, and a prognostic role of AMC was observed in non-Asian patients (HR: 1.274, 95% CI: 1.145-1.454; $p < 0.001$), patients with colorectal cancer (HR: 1.487; 95% CI: 1.259-1.756; $p < 0.001$) and lung cancer (HR: 1.381; 95% CI: 1.161-1.642; $p < 0.001$), patients with stage IV cancer (HR: 1.640; 95% CI: 1.361-1.975; $p < 0.001$) with no heterogeneity. The adverse effect of higher AMC was also seen when stratified by sample size, cut-off value, distant metastatic status, the time of blood testing, analysis method, and study quality (Table 2).

### 3.5 Cancer-specific survival

Ten studies involving 2,315 patients reported suitable data for CSS analysis. Overall, an increase in the monocyte
| Variables                        | N<sup>a</sup> | Case<sup>b</sup> | Pooled data | Heterogeneity | Meta-regression <br>(p value) |
|---------------------------------|---------------|------------------|-------------|---------------|--------------------------|
|                                 |               |                  | HR (95% CI) | P             | I²            | Ph           |                |
| Overall survival                | 88            | 29,130           | 1.615 (1.475-1.768) | <0.001 | 83.50%       | <0.001       |
| By region                       |               |                  |             |               |              |              |                |
| Asian                           | 70            | 23,730           | 1.589 (1.462-1.728) | <0.001 | 53.90%       | <0.001       | 0.791         |
| Non-Asian                       | 18            | 5400             | 1.580 (1.307-1.910) | <0.001 | 86.40%       | <0.001       | N. E.         |
| By sample size                  |               |                  |             |               |              |              |                |
| >200                            | 46            | 23,899           | 1.560 (1.431-1.700) | <0.001 | 52.30%       | 0.001        | 0.886         |
| ≤200                            | 42            | 5231             | 1.640 (1.419-1.895) | <0.001 | 80.20%       | <0.001       | N. E.         |
| By cut-off value                |               |                  |             |               |              |              |                |
| >500                            | 37            | 13,786           | 1.657 (1.440-1.907) | <0.001 | 84.50%       | <0.001       | 0.664         |
| ≤500                            | 48            | 14,728           | 1.543 (1.401-1.700) | <0.001 | 49.50%       | <0.001       | 0.543         |
| NA                              | 2             | 616              | 1.750 (1.475-2.077) | <0.001 | 0%           | 0.699        | N. E.         |
| By cancer type                  |               |                  |             |               |              |              |                |
| Bile duct cancer                | 2             | 308              | 1.427 (0.984-2.070) | 0.061 | 24.90%       | 0.249        | 0.428         |
| Breast cancer                   | 6             | 2863             | 1.564 (1.023-2.391) | 0.039 | 31.50%       | 0.199        | 0.464         |
| Cervical cancer                 | 6             | 2106             | 2.917 (1.186-7.175) | 0.020 | 83.90%       | <0.001       | 0.571         |
| Colorectal cancer               | 17            | 4709             | 1.689 (1.456-1.958) | <0.001 | 31.80%       | 0.102        | 0.533         |
| Endometrial cancer              | 2             | 851              | 1.777 (0.880-3.588) | 0.109 | 66.20%       | 0.085        | 0.598         |
| Esophageal cancer               | 5             | 1293             | 1.614 (1.268-2.053) | <0.001 | 25.20%       | 0.253        | 0.543         |
| Gallbladder cancer              | 1             | 34               | 0.800 (0.114-5.632) | 0.823 | 0.376        |              |              |
| Gastric cancer                  | 8             | 5812             | 1.181 (0.978-1.426) | 0.084 | 56.50%       | 0.024        | 0.233         |
| Gynecological cancer            | 1             | 259              | 1.400 (1.049-1.869) | 0.022 | 0.404        |              |              |
| Hepatocellular cancer           | 4             | 784              | 1.551 (1.292-1.861) | <0.001 | 19.70%       | 0.291        | 0.496         |
| Head and neck cancer            | 9             | 4293             | 1.530 (1.265-1.850) | <0.001 | 59.00%       | 0.009        | 0.439         |
| Lung cancer                     | 10            | 2004             | 1.654 (1.265-2.162) | <0.001 | 58.90%       | 0.009        | 0.499         |
| Melanoma                        | 6             | 2197             | 1.644 (1.325-2.040) | <0.001 | 46.40%       | 0.097        | 0.519         |
| MPM                             | 2             | 397              | 1.663 (0.771-3.589) | 0.195 | 70.20%       | 0.067        | 0.479         |
| Pancreatic cancer               | 3             | 465              | 1.731 (1.404-2.135) | <0.001 | 6.60%        | 0.343        | 0.565         |
| Prostate cancer                 | 3             | 504              | 2.253 (1.665-3.048) | <0.001 | 0%           | 0.463        | 0.903         |
| Renal cell cancer               | 1             | 58               | 2.470 (0.937-6.508) | 0.067 |              |              | N. E.         |
| Unknown malignant cancer        | 1             | 193              | 1.567 (1.023-2.399) | 0.039 |              |              | 0.516         |
| By primary tumor site           |               |                  |             |               |              |              |                |
| Abdominal cancers               | 36            | 12,170           | 1.510 (1.366-1.671) | <0.001 | 50.20%       | <0.001       | 0.598         |
| Head and neck cancers           | 10            | 4293             | 1.530 (1.265-1.850) | <0.001 | 59.00%       | 0.009        | 0.704         |
| Thoracic cancers                | 23            | 6557             | 1.609 (1.381-1.876) | <0.001 | 42.60%       | 0.017        | 0.934         |
| Pelvic cancers                  | 12            | 3720             | 2.111 (1.480-3.011) | <0.001 | 85.30%       | <0.001       | 0.581         |
| Other cancers                   | 7             | 2390             | 1.628 (1.359-1.950) | <0.001 | 35.80%       | 0.155        | N. E.         |
| By distant metastasis (DM)      |               |                  |             |               |              |              |                |
| No DM                           | 38            | 17,142           | 1.553 (1.361-1.773) | <0.001 | 80.80%       | <0.001       | 0.349         |
| DM                              | 15            | 3133             | 1.554 (1.313-1.839) | <0.001 | 66.40%       | <0.001       | 0.445         |
| Both                            | 30            | 7404             | 1.609 (1.450-1.784) | <0.001 | 28.80%       | 0.073        | 0.617         |
| NA                              | 5             | 1451             | 1.780 (1.329-2.385) | <0.001 | 27.40%       | 0.239        | N. E.         |

(Continues)
### TABLE 2 (Continued)

| Variables                        | N^a | Case^b | HR (95% CI) | P   | I^2   | Ph   | Meta-regression (p value) |
|----------------------------------|-----|--------|-------------|-----|-------|------|----------------------------|
| **By TNM stage**                 |     |        |             |     |       |      |                            |
| <IV                              | 28  | 13,268 | 1.513 (1.316-1.738) | <0.001 | 62.00% | <0.001 | 0.443                      |
| IV                               | 15  | 3133   | 1.554 (1.313-1.839)  | <0.001 | 66.40% | <0.001 | 0.611                      |
| I-IV                             | 37  | 11,457 | 1.693 (1.464-1.958)  | <0.001 | 81.00% | <0.001 | 0.837                      |
| NA                               | 8   | 1254   | 1.615 (1.374-1.898)  | <0.001 | 0%     | 0.433 | N. E.                      |
| **By the time of blood testing** |     |        |             |     |       |      |                            |
| Pre-treatment                    | 52  | 13,024 | 1.596 (1.418-1.795)  | <0.001 | 84.70% | <0.001 | 0.538                      |
| Pre-operative                    | 34  | 15,923 | 1.596 (1.418-1.796)  | <0.001 | 53.40% | <0.001 | 0.550                      |
| Post-operative                   | 1   | 34     | 0.800 (0.114-5.632)   | 0.823 |       |      | N. E.                      |
| NA                               | 1   | 149    | 2.860 (1.377-5.939)   | 0.005 |       |      | 0.294                      |
| **By analysis method**           |     |        |             |     |       |      |                            |
| MV                               | 46  | 19,650 | 1.660 (1.495-1.843)  | <0.001 | 57.80% | <0.001 | 0.244                      |
| UV                               | 42  | 9480   | 1.524 (1.344-1.728)  | <0.001 | 81.60% | <0.001 | N. E.                      |
| **By NOS score**                 |     |        |             |     |       |      |                            |
| High quality                     | 52  | 15,300 | 1.596 (1.414-1.800)  | <0.001 | 80.70% | <0.001 | N. E.                      |
| Low quality                      | 36  | 13,830 | 1.590 (1.441-1.754)  | <0.001 | 50.50% | <0.001 | 0.680                      |
| **Disease-free survival**        |     |        |             |     |       |      |                            |
| Overall                          | 41  | 11,514 | 1.488 (1.357-1.633)  | <0.001 | 32.00% | 0.028 |                            |
| **By region**                    |     |        |             |     |       |      |                            |
| Asian                            | 35  | 9734   | 1.478 (1.329-1.644)  | <0.001 | 39.80% | 0.009 | N. E.                      |
| Non-Asian                        | 6   | 1780   | 1.648 (1.335-2.036)  | <0.001 | 0%     | 0.996 | 0.394                      |
| **By sample size**               |     |        |             |     |       |      |                            |
| >200                             | 21  | 9170   | 1.499 (1.304-1.723)  | <0.001 | 48.90% | 0.006 | N. E.                      |
| ≤200                             | 20  | 2344   | 1.452 (1.301-1.621)  | <0.001 | 3.30%  | 0.415 | 0.803                      |
| **By cut-off value**             |     |        |             |     |       |      |                            |
| >500                             | 12  | 3679   | 1.538 (1.357-1.744)  | <0.001 | 0%     | 0.506 | 0.312                      |
| ≤500                             | 29  | 7835   | 1.453 (1.286-1.642)  | <0.001 | 40.00% | 0.015 | N. E.                      |
| **By cancer**                    |     |        |             |     |       |      |                            |
| Breast cancer                    | 9   | 1550   | 1.465 (1.129-1.900)  | <0.001 | 0%     | 0.646 | 0.043                      |
| Cervical cancer                  | 1   | 125    | 2.076 (1.063-4.053)  | 0.032 |       |      | 0.160                      |
| Colorectal cancer                | 6   | 1857   | 1.738 (1.279-2.362)  | <0.001 | 42.70% | 0.120 | 0.063                      |
| Endometrial cancer               | 2   | 851    | 1.669 (1.213-2.295)  | <0.001 | 0%     | 0.847 | 0.067                      |
| Esophageal cancer                | 3   | 1124   | 1.331 (1.077-1.643)  | 0.002 | 0%     | 0.403 | 0.031                      |
| Extrahepatic bile duct cancer    | 1   | 121    | 1.939 (1.047-3.591)  | 0.048 |       |      | 0.130                      |
| Gallbladder cancer               | 1   | 34     | 2.084 (0.529-8.218)  | 0.294 |       |      | 0.280                      |
| Gastric cancer                   | 2   | 460    | 0.805 (0.536-1.209)  | 0.295 | 48.50% | 0.163 | 0.006                      |
| Hepatocellular cancer            | 4   | 906    | 1.536 (1.116-2.112)  | 0.008 | 65.70% | 0.033 | 0.033                      |
| Head and neck cancer             | 6   | 3132   | 1.570 (1.291-1.909)  | 0.026 | 32.70% | 0.191 | 0.043                      |
| Lung cancer                      | 2   | 735    | 1.474 (1.152-1.888)  | 0.006 | 0%     | 0.417 | 0.045                      |
| Melanoma                         | 2   | 227    | 1.530 (1.004-2.332)  | 0.048 | 0%     | 0.907 | 0.056                      |
| Pancreatic cancer                | 1   | 144    | 1.471 (1.014-2.135)  | 0.042 |       |      | 0.048                      |
| Prostate cancer                  | 1   | 248    | 1.894 (0.998-3.595)  | 0.051 |       |      | 0.126                      |

(Continues)
### TABLE 2 (Continued)

| Variables                        | N<sup>a</sup> | Case<sup>b</sup> | Pooled data (HR [95% CI]) | Heterogeneity | Meta-regression (p value) |
|----------------------------------|---------------|-----------------|--------------------------|---------------|-------------------------|
|                                  |               |                 |                          | I<sup>2</sup> | P<sub>H</sub> |
| **By primary tumor site**        |               |                 |                          |               |                         |
| Head and neck cancers            | 5             | 3016            | 1.585 (1.203-2.088)      | 0.001         | 41.60% 0.144 N. E.     |
| Thoracic cancers                 | 13            | 2867            | 1.418 (1.226-1.641)      | <0.001        | 0% 0.709 0.703         |
| Abdominal cancers                | 16            | 3638            | 1.489 (1.244-1.782)      | <0.001        | 61.90% 0.001 0.610     |
| Pelvic cancers                   | 5             | 1766            | 1.623 (1.305-2.017)      | <0.001        | 0% 0.800 0.798         |
| Other cancers                    | 2             | 227             | 1.530 (1.004-2.332)      | 0.048         | 0% 0.907 0.937         |
| **By distant metastasis (DM) status** |               |                 |                          |               |                         |
| No DM                            | 30            | 8196            | 1.468 (1.312-1.642)      | <0.001        | 41.40% 0.010 0.455     |
| DM                               | 1             | 89              | 1.143 (0.694-1.883)      | 0.600         | N. E.                  |
| Both                             | 7             | 1986            | 1.627 (1.315-2.013)      | <0.001        | 0% 0.518 0.282         |
| NA                               | 3             | 1243            | 1.727 (1.269-2.351)      | 0.001         | 0% 0.932 0.270         |
| **By TNM stage**                 |               |                 |                          |               |                         |
| <IV stage                        | 9             | 4743            | 1.436 (1.239-1.664)      | <0.001        | 42.00% 0.026 0.703     |
| IV stage                         | 2             | 163             | 1.279 (0.855-1.914)      | 0.231         | 0% 0.453 N. E.         |
| I-IV stage                       | 7             | 6019            | 1.524 (1.359-1.710)      | <0.001        | 1.30% 0.436 0.411      |
| NA                               | 4             | 589             | 1.931 (1.066-3.498)      | 0.030         | 66.80% 0.029 0.555     |
| **By the time of blood testing** |               |                 |                          |               |                         |
| Pre-treatment                    | 12            | 4092            | 1.498 (1.323-1.697)      | <0.001        | 0% 0.859 0.688         |
| Pre-operative                    | 28            | 7388            | 1.500 (1.321-1.703)      | <0.001        | 47.60% 0.003 0.692     |
| Post-operative                   | 1             | 34              | 2.084 (0.529-8.218)      | 0.294         | N. E.                  |
| **By analysis method**           |               |                 |                          |               |                         |
| MV                               | 16            | 6277            | 1.420 (1.248-1.616)      | <0.001        | 44.40% 0.029 0.274     |
| UV                               | 25            | 5237            | 1.566 (1.375-1.784)      | <0.001        | 18.10% 0.209 N. E.     |
| **By NOS score**                 |               |                 |                          |               |                         |
| High quality                     | 29            | 7126            | 1.438 (1.293-1.599)      | <0.001        | 32.50% 0.048 0.236     |
| Low quality                      | 12            | 4388            | 1.665 (1.371-2.021)      | <0.001        | 31.10% 0.142 N. E.     |
| **Progressive-free survival**    |               |                 |                          |               |                         |
| Overall                          | 23            | 5126            | 1.533 (1.342-1.751)      | <0.001        | 45.50% 0.010           |
| **By region**                    |               |                 |                          |               |                         |
| Asian                            | 16            | 3852            | 1.672 (1.380-2.026)      | <0.001        | 48.60% 0.015 0.126     |
| Non-Asian                        | 7             | 1274            | 1.290 (1.145-1.454)      | <0.001        | 0% 0.531 N. E.         |
| **By sample size**               |               |                 |                          |               |                         |
| >200                             | 10            | 3769            | 1.655 (1.348-2.031)      | <0.001        | 50.50% 0.033 0.409     |
| ≤200                             | 13            | 1357            | 1.442 (1.209-1.720)      | <0.001        | 38.30% 0.078 N. E.     |
| **By cut-off value**             |               |                 |                          |               |                         |
| >500                             | 13            | 2359            | 1.439 (1.184-1.749)      | <0.001        | 54.60% 0.009 0.967     |
| ≤500                             | 9             | 2472            | 1.700 (1.442-2.004)      | <0.001        | 1.30% 0.423 N. E.      |
| NA                               | 1             | 295             | 1.380 (1.062-1.793)      | 0.016         | N. E.                  |
| **By cancer type**               |               |                 |                          |               |                         |
| Cervical cancer                  | 5             | 1981            | 2.338 (1.091-5.011)      | 0.029         | 81.90% <0.001 0.460    |
| Colorectal cancer                | 4             | 1094            | 1.487 (1.259-1.756)      | <0.001        | 0% 0.667 0.610         |
| Endometrial cancer               | 1             | 310             | 1.397 (0.938-2.080)      | 0.100         | 0.471                  |
| Esophageal cancer                | 1             | 126             | 1.900 (1.110-3.251)      | 0.019         | 0.761                  |

(Continues)
| Variables                      | N<sup>a</sup> | Case<sup>b</sup> | Pooled data HR (95% CI) | P   | $i^2$ | $P_{HI}$ | Meta-regression (p value) |
|-------------------------------|-------------|---------------|------------------------|-----|-------|---------|--------------------------|
| Head and neck cancer         | 1           | 75            | 2.923 (1.214-7.036)    | 0.017 |       |         | 0.259                    |
| Lung cancer                   | 6           | 921           | 1.381 (1.161-1.642)    | <0.001 | 0%    | 0.445   | 0.805                    |
| Pancreatic cancer             | 1           | 57            | 1.188 (0.419-3.369)    | 0.746 |       |         | 0.963                    |
| Prostate cancer               | 3           | 504           | 1.791 (1.310-2.449)    | <0.001 | 33.20% | 0.224   | 0.439                    |
| Renal cell cancer             | 1           | 58            | 1.140 (0.521-2.497)    | 0.743 |       |         | N. E.                    |

By primary tumor site

| Head and neck cancers         | 1           | 75            | 2.923 (1.214-7.036)    | 0.017 |       |         | 0.176                    |
| Thoracic cancers              | 6           | 921           | 1.318 (1.161-1.642)    | <0.001 | 0%    | 0.445   | N. E.                    |
| Abdominal cancers             | 7           | 1335          | 1.494 (1.281-1.743)    | <0.001 | 61.90% | 0.811   | 0.501                    |
| Pelvic cancers                | 9           | 2795          | 1.842 (1.339-2.533)    | <0.001 | 72.80% | <0.001  | 0.248                    |

By distant metastatic status

| No DM                        | 7           | 2025          | 1.876 (1.173-3.000)    | 0.009 |       |         | 72.20% 0.001  N. E.     |
| DM                           | 5           | 855           | 1.640 (1.361-1.975)    | <0.001 | 0%    | 0.423   | 0.736                    |
| Both                         | 11          | 2246          | 1.436 (1.253-1.646)    | <0.001 | 12.20% | 0.328   | 0.694                    |

By TNM stage

| <IV                          | 3           | 506           | 2.892 (0.945-8.850)    | 0.063 |       |         | 75.80% 0.016  N. E.     |
| IV                           | 5           | 855           | 1.640 (1.361-1.975)    | <0.001 | 0%    | 0.423   | 0.250                    |
| I-IV                         | 13          | 3482          | 1.378 (1.187-1.600)    | <0.001 | 33.90% | 0.111   | 0.077                    |
| NA                           | 2           | 283           | 1.608 (1.202-2.152)    | 0.001 | 0%    | 0.469   | 0.265                    |

By the time of blood testing

| Pre-treatment                | 20          | 4367          | 1.469 (1.302-1.658)    | <0.001 |       |         | 30.90% 0.094  0.272     |
| Pre-operative                | 3           | 759           | 2.717 (1.093-6.757)    | 0.032 |       |         | 81.30% 0.005  N. E.     |

By analysis method

| MV                           | 13          | 3334          | 1.762 (1.478-2.102)    | <0.001 |       |         | 35.90% 0.095  0.011     |
| UV                           | 10          | 1792          | 1.276 (1.112-1.465)    | 0.001 |       |         | 14.00% 0.314  N. E.     |

By NOS score

| High quality                 | 14          | 1992          | 1.396 (1.221-1.596)    | <0.001 |       |         | 23.70% 0.198  0.172     |
| Low quality                  | 9           | 3134          | 1.805 (1.377-2.366)    | <0.001 |       |         | 56.50% 0.019  N. E.     |

Cancer-specific survival

| <0.001                       | 57.00%      | 0.013         | 1.585 (1.253-2.006)    |

By region

| Asian                        | 7           | 1780          | 1.593 (1.179-2.152)    | 0.002 |       |         | 64.90% 0.009  0.952     |
| Non-Asian                    | 3           | 535           | 1.621 (1.055-2.491)    | 0.028 |       |         | 41.30% 0.182  N. E.     |

By sample size

| >200                         | 5           | 1590          | 1.780 (1.197-2.648)    | 0.004 |       |         | 62.80% 0.029  N. E.     |
| ≤200                         | 5           | 725           | 1.454 (1.074-1.970)    | 0.016 |       |         | 52.80% 0.076  0.549     |

By cut-off value

| >500                         | 5           | 1080          | 1.484 (1.195-1.843)    | <0.001 |       |         | 9.30% 0.353  0.754      |
| ≤500                         | 5           | 1235          | 1.772 (1.106-2.839)    | 0.017 |       |         | 75.20% 0.003  N. E.     |

By cancer type

| Colorectal cancer            | 5           | 1080          | 1.524 (1.209-1.921)    | <0.001 |       |         | 0%  0.482  0.651       |
| Hepatocellular cancer        | 1           | 198           | 1.070 (0.835-1.371)    | 0.593 |       |         | 0.369                    |

(Continues)
showed associations with worse CSS (*HR*: 1.585; 95% *CI*: 1.253-2.006; *p* < 0.001) (Table 2; Figure 4). A relatively high heterogeneity was observed across the studies (*I^2* = 57.00%; *p* = 0.013). When stratified by cancer type, distant metastatic status, and the time of blood testing, elevated AMC was associated with worse outcome in patients with colorectal cancer (*HR*: 1.523; 95% *CI*: 1.209-1.921; *p* < 0.001), distant metastatic cancer (*HR*: 1.508; 95% *CI*: 1.208-1.881; *p* < 0.001) and studies with pre-operative AMC (*HR*: 1.253; 95% *CI*: 1.066-1.473; *p* = 0.006) without heterogeneity. The subgroup analyses also revealed that elevated AMC might be a potential biomarker in non-Asian patients, studies with high cut-off value, and studies with univariate analysis or low quality (Table 2).

### 3.6 Relationships of AMC and clinical features

Association between monocyte count and clinicopathological parameters were evaluated among 28 studies. There was a significantly positive associations between elevated AMC and advanced T stage (*OR*:1.298; 95% *CI*:1.035-1.629; *p* = 0.024), microvascular invasion
The pooled analysis revealed that the AMC of male with solid tumors was more likely higher (OR: 2.147; 95% CI: 1.650-2.795, p < 0.001). (Table 3, Figure S1) We also evaluated that smoking was positively associated with higher AMC (OR: 1.684, 95% CI: 1.104-2.570, p = 0.016). Patients with elevated pre-operative monocyte has lower albumin (SMD: 0.264; 95% CI: 0.084-0.444; p = 0.004), while higher platelet (SMD: 0.455; 95% CI: 0.166-0.743; p = 0.002) (Table 3).

### 3.7 Publication bias and sensitivity analysis

For OS, the funnel plot was visibly asymmetrical, indicating the presence of publication bias (Figure S2). In accord with the plot, the results of Begg's test (p = 0.028) and Egger's test (p < 0.001) further confirmed that the asymmetry was mainly attributed to the publication bias. The “trim-and-fill” analysis was performed and no significant change in our results was found, further suggesting the stability of the meta-analysis (HR: 1.461; 95% CI: 1.343-1.588; p < 0.001) (Supplementary Figure 3). For DFS, the results of Begg's test (p = 0.003) and Egger's test (p = 0.001) showed publication bias. The adjusted random effect HR of 1.363 (95% CI: 1.234-1.506, p < 0.001) was obtained using the “trim-and-fill” analysis, which was consistent with the primary analysis. For PFS, there were no evidence of asymmetry, and no trimming was performed after applying the “trim-and-fill” analysis. For CSS, the results of Begg's test (p = 0.007) and Egger's test (p = 0.001) indicated publication bias, and there was no trimming performed after applying the “trim-and-fill” analysis.

In addition, sensitivity analysis was carried out and the results showed that the pooled HRs were not significantly affected by omitting an individual study.

### 4 DISCUSSION

To the best of our knowledge, we performed a comprehensive meta-analysis for the first time to assess the prognostic value of AMC in various solid tumors. The systematic review and meta-analysis involving data on 32,229
participants from 104 studies provided robust evidence that elevated the level of monocyte count might be an independent prognostic factor for poor OS, DFS, PFS, and CSS in non-hematologic tumors. Subgroup analyses focused on clinical outcomes were conducted and further proved the predictor role of elevated AMC on long-term cancer outcomes. In addition, we found a tendency that an elevated AMC was significantly associated with some clinicopathological characteristics including gender, T stage, vascular invasion, tumor length, and smoking, as well as higher platelet counts and lower albumin.

Since Virchow described the role of inflammation in 1863, inflammatory response has gone beyond the marker of infection. It has been hypothesized that cancer arises from the background of inflammation, which has been supported by a multitude of evidence in the last decade.\textsuperscript{10–12} So far, it has been widely accepted that the inflammatory components, which constitute a major part of the TME, may be triggered by the conditions that predispose to cancer or by genetic events.\textsuperscript{6} What is more, as a binary “anti-tumor” or “pro-tumor” environment, the dominant function of TME is determined by the cross-regulation of immune cells and

| Variables | Studies | Patients | Pooled OR | 95% CI       | p value*a | Heterogeneity \(I^2\) | Ph value** |
|-----------|---------|----------|-----------|--------------|-----------|------------------------|-----------|
| Gender (male vs. female) | 19 | 4340 | 2.147 | 1.650-2.795 | <0.001 | 65.50% | <0.001 |
| APF (high vs. low) | 5 | 1102 | 1.265 | 0.965-1.659 | 0.089 | 4.60% | 0.381 |
| Distant metastasis | 5 | 1405 | 1.179 | 0.921-1.510 | 0.192 | 0% | 0.718 |
| T stage (T2+ vs. <T2) | 9 | 4222 | 1.298 | 1.035-1.629 | 0.024 | 18.70% | 0.277 |
| N stage (N1+ vs. NO) | 9 | 4324 | 1.080 | 0.910-1.281 | 0.379 | 20.00% | 0.265 |
| TMN stage (III+IV vs. I+II) | 9 | 2503 | 1.224 | 0.950-1.576 | 0.118 | 47.50% | 0.055 |
| Microvascular invasion (yes vs. no) | 3 | 555 | 1.896 | 1.240-2.900 | 0.003 | 0% | 0.620 |
| Macrophage invasion (yes vs. no) | 2 | 452 | 4.713 | 1.293-17.177 | 0.019 | 83.90% | 0.013 |
| Vascular invasion (yes vs. no) | 3 | 740 | 1.580 | 0.975-2.561 | 0.063 | 0% | 0.700 |
| Lymphatic permeation (yes vs. no) | 2 | 520 | 0.943 | 0.537-1.655 | 0.837 | 18.80% | 0.267 |
| Tumor length (high vs. low) | 8 | 1520 | 1.783 | 1.378-2.308 | <0.001 | 8.20% | 0.367 |
| Differentiation (well vs. poor/moderate) | 10 | 2625 | 0.968 | 0.784-1.196 | 0.762 | 9.40% | 0.356 |
| Adjuvant therapy\textsuperscript{a} | 6 | 1422 | 0.900 | 0.715-1.133 | 0.370 | 0% | 0.670 |
| Adjuvant therapy\textsuperscript{b} | 3 | 883 | 0.905 | 0.675-1.214 | 0.505 | 0% | 0.651 |
| Smoking (yes vs. no) | 6 | 1858 | 1.684 | 1.104-2.570 | 0.016 | 72.80% | 0.002 |
| Continuous variables | | | | | | | |
| Age | 11 | 3072 | 0.019 | −0.077-0.116 | 0.693 | 39.10% | 0.088 |
| Hemoglobin | 4 | 1025 | 0.004 | −0.119-0.128 | 0.946 | 0% | 0.707 |
| Platelet | 4 | 1008 | 0.455 | 0.166-0.743 | 0.002 | 72.00% | 0.013 |
| Albumin (low vs. high) | 3 | 790 | 0.264 | 0.084-0.444 | 0.004 | 0% | 0.471 |
| Hematocrit | 3 | 807 | −0.014 | −0.156-0.124 | 0.841 | 0% | 0.690 |

OR: odd ratio; SMD: standardized mean difference; CI: confidence interval; \(I^2\): the value of I-squared statistics; vs.: versus.

\textsuperscript{a}Studies with adjuvant therapy versus studies without adjuvant therapy.

\textsuperscript{b}Studies with radiotherapy versus studies with concurrent chemoradiotherapy.

\*p value of pooled HR.

\**p value of Heterogeneity test.

\***p value of SMD.
non-immune cells by perceiving signaling molecules to induce the proliferative activity of the tumor, metastasis, cell migration, and immune response against therapy. Recent research efforts have shed light on the prognostic significance of immune cells in various cancers.

Of these immune cells, monocytes are a subset of circulating blood cell originated from myeloid progenitors in the bone marrow and subsequently can be attracted to peripheral tissues via bloodstream. Circulating monocytes perform versatile functions both in antimicrobial defense and chronic inflammation. In TME, peripheral monocytes constantly enter the tumor sites and inhibit the tumor-related immune defense function by expressing inhibitory molecules and/or releasing soluble inhibitory factors via tumor-derived signals. As monocyte measurement is easily standardized and available in blood routine examination, monocyte could be a potentially helpful and convenient serum biomarker in clinical practice even be added as a new item in the immnoscore system. The qualitative and quantitative changes of the monocyte count in tumor have been attracting research attention. In accordance with our finding, recent meta-analyses also pooled the data of individual tumor types and demonstrated that elevated peripheral monocyte appeared to be synonymous with an increased risk of mortality in the context of several malignancies. However, the effect of elevated AMC on outcomes has not been synthetically and comprehensively analyzed in solid tumors and the variation of the effects according to tumor type has not been explained. In addition, the direct evidence for some cancers, such as melanoma and malignant pleural mesothelioma, was sparse due to limited studies and small sample sizes. Therefore, we conducted the present meta-analysis to sort through currently available data and concluded that elevated AMC was associated with poor clinical outcomes in non-hematologic tumors.

The exact underlying mechanisms of the association between elevated AMC and unfavorable outcomes have not been fully clarified and might be multifactorial. It is recognized that monocytes originate from mononuclear myeloid cells in bone marrow, which come into play in response to pathogenic stimuli such as cancer by myelopoiesis which largely manifest in the expansion of monocytes and neutrophils. In the study, our results aggregated previous studies and revealed the positive associations between elevated AMC and local invasion of tumor cells and tumor length. Besides, TAMs play a vital role at the crossroads of inflammation and cancer. Monocytes travel to peripheral tissue and move directionally to the tumor sites owing to tumor-derived signals, subsequently differentiate to TAMs. Anti-tumor M1 macrophages are characterized by the induction of lipopolysaccharide (LPS) and IFN-γ, and are able to withstand intracellular pathogens and cancer cells. In contrast, polarized pro-tumor M2 macrophages are a source and target of a distinct pattern of cytokines, chemokines, and growth factors generally exerting tumor-promoting and immune escape effects, and impairs anticancer therapies. Therefore, the understanding of the balance between M1 and M2 polarization provides a theoretical foundation for better rational manipulation of monocytes differentiation and macrophage polarization switching in TME. Monocyte subpopulations have different functions in TME. Previous study described that inflammatory monocytes could be predominantly divided into classical inflammatory monocytes (CCR2<sup>high</sup>Ly6C<sup>++</sup>CD43<sup>+</sup>) in mice, homologous to CCR2<sup>high</sup>CD14<sup>++</sup>CD16<sup>+</sup> in human), intermediate monocytes (Ly6C<sup>++</sup>CD43<sup>++</sup> in mice, homologous to CD14<sup>++</sup>CD16<sup>+</sup> in human) and nonclassical patrolling monocytes (CX<sub>3</sub>CR<sub>1</sub><sup>high</sup>Ly6C<sup>++</sup>CD43<sup>++</sup>) in mice, homologous to CX<sub>3</sub>CR<sub>1</sub><sup>high</sup>CD14<sup>++</sup>CD16<sup>+</sup> in human). (The + denotes an expression level that is 10-fold above the isotype control and ++ is 100-fold above the isotype control).

In addition, the monocyte chemotactic factor monocyte chemoattractant protein-1 (C-C chemokine ligand 2 (MCP-1/CCL2) secreted by tumor cells is a chemokine with potent monocyte chemotactic activity via binding to CCR2 (the receptor for chemokine CCL2), has been shown to directly or indirectly enhance immunosuppression and metastasis by vascular endothelial growth factor (VEGF) secretion and other tumor-secreted factors like IFNγ in murine cancer models. Yoshimura T. expatiated on the correlation between MCP-1 production and TAMs and indicated that MCP-1 production regulated the vicious cycle between host cells and tumor cells thus promoting cancer progression. Additionally, recent studies reported the NK cell-monocyte interactions enhanced NK cell antitumor activity in cancer prognosis and the response to monoclonal antibody therapy. It has been reported that tumor-infiltrating monocytes/macrophages induced NK cell dysfunction via TGFβ1, thus impairing the expression of IFNα, TNFγ, and Ki-67 in tumor progression in gastric cancer. Kubo et al. also demonstrated that patrolling monocytes contributing to the prevention of primary tumor by producing IL-15, which is the key mediator to activate the anti-metastatic role of NK cells. Moreover, myeloid-derived suppressor cells (MDSCs) generated from myeloid cells in TME and were similar but functionally distinct from monocytes and neutrophils. Chae et al. demonstrated that MDSC could also arose directly from monocytes and displayed the immune suppressive activity in tumor.
progression in the murine model. However, cells with MDSC features could be easily mistaken for monocytes in some studies. Otherwise, Kuang et al. found monocytes activated by tumors strongly express programmed cell death ligand 1 (PD-L1) and effectively suppress tumor-specific T cell immunity in HCC in vivo. Taube et al. also demonstrated some factors such as IL-10 and IL-32γ induced PD-L1 expression on monocytes in melanoma. Therefore, the PD-L1 expression on the monocytes could be a novel mechanism explaining the association between monocyte and cancer. All the proposed mechanisms about monocyte might inspire potential molecular targets for personalized treatment strategy of solid tumors.

It has been reported that a therapeutic regimen such as chemotherapy could modulate the pro-tumor and anti-tumor ability of monocytes/macrophages lineages. Different oncotherapy regimens have been supposed to be associated with various changes in the biology and function of these cells. In the subgroup analyses, nevertheless, studies on the prognostic value of AMC in patients with different treatments have not been evaluated due to the variety and complexity of treatment programs. In addition, our meta-analysis has demonstrated that elevated AMC was associated with poor prognosis. However, a precise cut-off value in clinical practice is a matter of broad discussion. At present, ROC curves were widely used in the threshold selection in diagnostic or screening tests considering the optimization of false-positive and false-negative interpretation. For this reason, most of the included studies chose ROC curves to define their threshold cut-off values. In the paper, we split studies with a cut-off >500 or ≤500, both studies with high cut-off and with low cut-off were associated with an increased risk of worse outcomes.

Our study possesses several strengths. Distinctively, we focused on all non-hematological tumors and provided comprehensive evidence for the prognostic value of AMC, which might be a weighted one involved in the immunoscore system. Moreover, because of the diversity of cancer types and studies, the research into subgroup analysis were lucubrated. It is the first time that pre-treatment AMC, pre-operative AMC, and post-operative AMC are compared. Based on subgroup analyses stratified by cut-off values of monocytes, higher cut-off values for OS and DFS seem to be more discriminative effective on prognosis, while inversely in PFS and CSS. Additionally, we studied the relationships between AMC and gender, T stage, tumor length, microvascular invasion, smoking, and other clinic parameters, which provide potential implications in clinical practice in the future.

Nevertheless, there were some limitations to the present study. A key limit was that cut-off levels of AMC were set based on ROC, median value, previous studies or other methods, making the routine application less practical. Although the cut-off >500/mm³ may enable us to better identify the poor outcomes in the present study, the optimal AMC cut-off awaits standardization. Besides, as Walker SP said, “the unpredictability of the diseases undermined the ability to plan ahead.” In practice, the dynamic change in prognostic indicators might be more valuable for one patient with solid tumor. Future studies on changes in cancer biomarkers and cut-off values defining the contributions of each cancer type are required. Additionally, we failed to find the sources of the heterogeneity of overall survival analyses with subgroup analyses and meta-regression analyses. Due to the variations of study quality and sample size among included studies, the statistical methods might be refined and a weighted mean might be computed. As mentioned before, publication bias existed in OS, DFS, and CSS analyses, and we were unable to extract the unreported data in some studies. Moreover, numerous confounding factors influence the post-operative AMC, such as surgical stress, bleeding, sepsis, even wound healing. Therefore, the prognostic value of post-operative AMC is relatively rarely reported. In addition, the relationships between monocyte and the features of tumor patients were not well defined in our study because of the lack of original data, hence the results may be less suitable in clinical practice.

5 | CONCLUSIONS

In conclusion, our comprehensive meta-analysis strongly supported that elevated AMC was remarkably associated with poor prognosis of patients with solid cancer. Monocyte, the relatively accessible low-cost cancer biomarker, could have widespread clinical implications for surgical management, treatment strategy, and prognosis assessment. Further multicenter studies in a randomized and prospective manner with optimal AMC cut-offs were warranted to refine our results and to advance the clinical applications of the monocyte counts in the future. Finally, given the different functions of monocyte subsets in TME, the monitoring of blood monocyte subpopulations could be further explored and applied to follow-up treatment response.

6 | DATA AVAILABLE STATEMENT

This study reports a systematic review for which all data are already available within the public realm in the form of scientific publications, references for which are provided.

ACKNOWLEDGMENT

We are particularly grateful to Deying Kang for his revision in the methodological section.
CONFLICTS OF INTEREST
The authors have declared no conflict of interest.

AUTHOR CONTRIBUTIONS
Shu Wen, Ying Hu, and Liangzhi Xu conceived and designed the experiments; Litalo Huang, Jin Peng, and Nan Chen collected the data; Meina Yang and Xiaoyang Shen analyzed the data; Shu Wen and Nan Chen contributed the materials/analysis tools and wrote the manuscript. Ying Hu and Song Yang revised the manuscript. All authors reviewed and approved the manuscript prior to submission.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Wen S, Chen N, Hu Y, et al. Elevated peripheral absolute monocyte count related to clinicopathological features and poor prognosis in solid tumors: Systematic review, meta-analysis, and meta-regression. Cancer Med. 2021;10:1690–1714. https://doi.org/10.1002/cam4.3773