Hyaluronic acid predicts poor prognosis in breast cancer patients
A protocol for systematic review and meta-analysis

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Abstract
Background: Hyaluronic acid (HA) may be a novel prognostic biomarker of breast cancer. However, the available evidence is controversial. Therefore, we performed a meta-analysis to determine the prognostic role of HA in breast cancer.

Methods: The data were extracted from seven articles by searching the databases of PubMed, EMBASE, Web of Science, the Chinese National Knowledge Infrastructure and Wanfang data for the prognostic role of HA in breast cancer. In reference to survival outcomes, the pooled hazard ratios (HRs) of HA were calculated given a 95% confidence interval (CI).

Results: A total of seven articles were included in our study involving 2664 cases. The result of meta-analysis showed that a high HA level predicts poor overall survival (OS) (HR=1.86, 95% CI: 1.28–2.71, P=.001) and shortened disease-free or recurrence-free survival or progression free survival (DFS/RFS/PFS) (HR=1.63, 95% CI: 1.14–2.33, P=.007) in breast cancer patients. Moreover, a high HA level in stroma (HR=1.63, 95% CI: 1.06–2.51, P=.025) and plasma (HR=3.26, 95% CI: 2.25–4.73, P<.001) significantly predicted poor OS. Besides, a tendency shows that HA was significantly correlated with lymph node metastasis (HR=1.55, 95% CI: 0.96–2.49, P=.070) and tumor grade (HR=2.10, 95% CI: 0.89–4.96, P=.089) on the clinical characteristics of patients.

Conclusion: These results suggested that HA has a potential to be prognostic biomarker in breast cancer patients, especially location in stroma and plasma.

Abbreviations: 95% CI = 95% confidence interval, DFS = disease-free survival, ECM = extracellular matrix, ER = estrogen receptor, GAG = glycosaminoglycan, HA = hyaluronic acid, HR = hazard ratio, OR = odds ratio, OS = overall survival, PFS = progression free survival, PR = progesterone receptor, RFS = recurrence-free survival.

Keywords: breast cancer, HA, meta-analysis, prognosis

1. Introduction
Breast cancer is both the most common malignancy and the leading cause of cancer death in the women’s world. In 2015 alone, 2.4 million new cases and 523,000 cancer-related deaths occurred.[1] In some Western countries, the mortality rate is declining because of early detection and adjuvant systemic therapies. However, in developing countries, breast cancer is more often diagnosed at a later stage, and long-term survival is poorer.[2,3] Although progress has been made in the treatments of breast cancer, its prognosis is still poor. Five-year survival is 85% in many Northern and Western European countries, while it is 60% in developing countries.[4] In the development, progression, and prognosis of breast cancer, it is very heterogeneous and complex. Despite there are a few biomarkers that have been developed, including circulating tumor cells (CTCs),[5] estrogen receptor (ER), progesterone receptor (PR), and p53,[6] novel tissue- or serum-based biomarkers that can be measured repeatedly to provide prognosis information are still needed.

Hyaluronic acid (HA) is the major glycosaminoglycan (GAG) in the extracellular matrix (ECM). D-glucurionate residue is linked through a β-(1→3) glycosidic bond with N-acetyl-D-glucosamine residue to form disaccharide. HA is formed with more than 2000 repeating disaccharides, which are linked together through a β-(1→4) glycosidic bond to form a giant
polysaccharide.[7] Because HA has no sulfate ester groups in other GAGs,[8,9] its molecule structure is relatively simple. However, several reports demonstrated that HA actively regulates cell adhesion, migration, proliferation,[10] and inflammatory diseases.[11–13] In addition, the high HA level in several types of solid tumors, such as bladder, prostate, breast, lung, and colon, is considered to be a malignant marker in clinic,[14–20] HA regulates the tumor microenvironment by interacting with specific receptors and intracellular signal transduction that promotes a malignant phenotype. Therefore, high levels of HA are identified in various cancer types (such as breast cancer, prostate cancer, lung cancer, and ovarian cancer).[21–23] Besides, several clinical studies have shown that HA promotes breast cancer cell invasion, motility and EMT by triggering various signaling pathways and by upregulating the expression of collagen degrading enzymes.[24–30] Recent accumulated evidence supports that a relationship between HA tumor expression and poor outcome in ovarian, gastric and breast carcinomas.[31,32] However, some of these studies have failed to confirm that HA is a potential prognostic biomarker for cancer. As a result, these researches in different tumor types remains controversial, and the consistency and magnitude of the prognostic value of HA expression remains enigmatic.[33–35] To verify its clinical relevance, we performed this meta-analysis systematically by integrating all published evidence to determine whether HA can predict poor survival in breast cancer patients.

2. Materials and methods

2.1. Search strategy and study selection

According to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and methods,[36] we carefully performed a systematical search of PubMed, EMBASE, Web of Science, the Chinese National Knowledge Infrastructure and Wanfang data for relevant articles up to September 6, 2019. The Medical Subjects Headings (MeSH) and the appropriate corresponding keywords were used: “breast cancer” or “breast tumor” or “breast neoplasm,” and “hyaluronan” or “hyaluronic acid.” The included studies met the following criteria:

1. the diagnosis of breast cancer was confirmed by pathological or mammography examination;
2. the level of HA in either tumor tissue or plasma was examined;
3. full text publication described the correlation between the HA level and overall survival (OS) and/or disease-free survival (DFS) and/or recurrence-free survival (RFS) and/or progression free survival (PFS); and
4. the publication language was confined to English.

The exclusive criteria were as follows: conference abstracts, letters, comments, reviews, or basic research articles; studies with duplicate data and repeat analyses and those without hazard ratio (HR), 95% confidence interval (95% CI), and P value, or useful data for the calculation from the data or graphical survival

Figure 1. Flow diagram of included study.
Table 1
Main characteristics of enrolled studies.

| Study       | Year | Country   | Ethnicity | Sample (number) | Stage (I + II), % | Type | Follow-up, months | HR       | Results   |
|-------------|------|-----------|-----------|-----------------|-------------------|------|-------------------|----------|-----------|
| Corte et al | 2006 | Spain     | Caucasian | Tumor (813)     | 59.3 (30–92)      | 70.9 | Mixed             | 57.4 (12–156) | OS/RFS   |
| Suwiat et al| 2004 | Australia | Caucasian | Stroma (79)     | 63 (28–32)        | 54.7 | Mixed             | 65.5 (11–116) | Reported |
| Auvinen et al | 2000 | Finland   | Caucasian | Stroma (143)    | 60 (27–91)        | 55.9 | Mixed             | 68.4 (37.2–99.6) | SC       |
| Casalini et al | 2008 | Italy     | Caucasian | Stroma (199)    | 53 (24–70)        | 79   | Mixed             | 120       | RFS      |
| Karihtala et al | 2007 | Finland   | Caucasian | Stroma (185)    | NM                | 50.4 | Mixed             | 68.4      | OS       |
| Peng et al (VC) | 2016 | Germany   | Caucasian | Plasma (73)     | 64 (67)           | NM   | Mixed             | 16.4 (4.6–121.2) | SC       |

DC = discovery cohort, DFS = disease-free survival, NM = not mentioned, OS = overall survival, PFS = progression-free survival, RFS = relapse-free survival, SC = survival curve, VC = validation cohort.

Table 2
Main results of enrolled studies.

| Study       | Method | Survival analysis | Sample        | Cut-off          | Conclusion | HR (95% CI) for OS | P       | HR (95% CI) for DFS/RFS/PFS | P       |
|-------------|--------|-------------------|---------------|------------------|------------|---------------------|---------|----------------------------|---------|
| Corte et al | IRMC   | U/KM              | Tumor         | median: 4966ng/mg | Negative   | 0.72 (0.48–1.10)    | .853    | 0.72 (0.45–1.15)            | .099    |
| Suwiat et al| ICS    | U                 | Stroma tumor  | 5%               | Negative   | 0.92 (0.29–2.97)    | .894    | 1.09 (0.43–2.77)            | .849    |
| Auvinen et al | ICS    | KM                | Stroma tumor  | 5%               | Positive   | 1.42 (0.71–2.81)    | .001    | 2.95 (1.24–7.05)            | .035    |
| Casalini et al | ICS    | U                 | Stroma tumor  | 33.3%            | Negative   | 1.84 (0.93–3.63)    | .01     | 1.00 (0.51–1.98)            | .176    |
| Karihtala et al | ICS   | KM                | Stroma       | NM               | Negative   | 1.71 (0.37–8.02)    | .075    | 1.39 (0.43–4.50)            | .09     |
| Peng et al (VC) | ICS    | U                 | Stroma tumor  | 5%               | Positive   | 2.25 (1.14–4.42)    | .01     | Positive                   | 2.53    |
| Peng et al (DC) | ELISA | M/KM             | Plasma Median: | 250ng/mL       | Positive   | 4.43 (2.01–9.76)    | 2.16 × 10^-4 | 2.25 (1.56–3.26) | 1.68 × 10^-5 |
| Peng et al (VC) | ELISA | Plasma           |               |                  | Positive   | 2.86 (1.55–5.29)    | .001    | 2.76 (1.51–5.05)            | .001    |

DC = discovery cohort, DFS = disease-free survival, ELISA = enzyme-linked immunosorbent assay, ICS = immunohistochemical staining, IRMC = immunoradiometric analysis, KM = Kaplan–Meier analysis, M = multivariate analysis, NM = not mentioned, OS = overall survival, PFS = progression-free survival, RFS = relapse-free survival, SC = survival curve, VC = validation cohort.

2.3. Statistical analysis

The HR with its variance estimates (95% CI) was estimated to evaluate the correlations between HA expression and breast cancer prognosis. The high expression and low expression of HA was defined according to the cut-off value provided in the article. The inter-study heterogeneity of the combined HRs was evaluated with Cochran’s Q test and the I² statistic. P < .05 or I² ≥ 50% indicated statistically heterogeneity, which was analyzed with the random-effects model. Otherwise, the fixed-effects model was employed. Subgroup analyzes were conducted to figure out the source of existing heterogeneity among results of different studies. HR values > 1 indicated significant associations with poor prognosis. Odds ratios (ORs) with 95% CI were used to examine the correlation between elevated expression of HA and the clinical variables in breast cancer. Publication bias was assessed using Egger linear regression test (P < .05 was considered as significant heterogeneity). Finally, sensitivity analysis was carried out by evaluating result stability after sequential omission of each study on the pooled outcomes. All statistical tests were conducted with STATA V12.0 software (Stata Corporation, College Station, TX).
Figure 2. The pooled HR of HA for overall survival and disease-free survival of breast cancer.
Figure 3. The pooled HR of HA for overall survival of breast cancer by subgroup analysis.

Table 3
Subgroup analyses of pooled hazard ratios for overall survival with elevated HA expression.

| Subgroup analysis | Data sets (number) | Number of samples | Model | HR (95% CI) | P    | Heterogeneity (I², P) |
|-------------------|--------------------|-------------------|-------|-------------|------|-----------------------|
| All               | 12                 | 2664              | Random| 1.86 (1.28–2.71) | .001 | 66.3%, .001           |
| Tumor             | 4                  | 1512              | Random| 1.22 (0.69–2.15)  | .497 | 65.0%, .036           |
| Stroma            | 4                  | 884               | Fixed | 1.63 (1.06–2.51)  | .025 | 0.0%, .582            |
| Plasma            | 4                  | 268               | Fixed | 3.26 (2.25–4.73)  | .000 | 0.0%, .700            |

NOTE: Weights are from random effects analysis.

Table 4
Meta-analyses of HA expression classified by clinicopathologic parameters.

| Variables                        | Number of studies | Number of samples | Model | OR (95% CI) | P    | Heterogeneity (I², P) |
|----------------------------------|-------------------|-------------------|-------|-------------|------|-----------------------|
| Tumor grade (III vs I/II)        | 6                 | 1381              | Random| 2.1 (0.89–4.96)  | .089 | 87.7%, P<.001         |
| Lymph node metastasis (positive vs negative) | 4                 | 1237              | Random| 1.55 (0.96–2.49)  | .07  | 56.8%, P=0.73         |
| PR status (positive vs negative) | 5                 | 1210              | Random| 0.56 (0.22–1.48)  | .243 | 86.5%, P<.001         |
| ER status (positive vs negative) | 5                 | 1200              | Random| 0.67 (0.29–1.55)  | .347 | 79.3%, P=.001         |
| tumor size (>2cm vs <2cm)        | 4                 | 1113              | Random| 1.61 (0.59–4.42)  | .356 | 82.1%, P=.001         |
| Distant metastases (absent vs present) | 2                 | 965               | Fixed | 1.27 (0.64–2.54)  | .491 | 24.3%, P=.248         |

95% CI=95% confidence interval, ER=estrogen receptor, OR=odds ratio, PR=progesterone receptor.
2.4. Ethics

This study was prepared according to PRISMA guidelines. We used publicly available data without involving human participants. Therefore, it does not require formal human research ethics committee review.

3. Results

3.1. Search results and main characteristics of included studies

The detailed flow diagram of screening process is showed in Figure 1. A total of 1855 records were initially identified in the databases of PubMed, EMBASE, Web of Science, the Chinese National Knowledge Infrastructure and Wanfang data, and 678 of them were excluded due to duplication. After titles and abstracts screened for eligibility, 669 articles were removed according to the exclusion criteria. Of the remaining 9 candidate articles enrolled for full-text articles screened, two articles did not provide the sufficient information for the extraction of HRs and 95% CI. As a result, 7 eligible articles, including 12 studies for OS, 10 studies for DFS/RFS/PFS, respectively, were considered in the meta-analysis. The included studies investigated a total of 2664 cases from Spain, Italy, Finland, and Germany, which composed with mixed histological type of breast cancer patients. The main characteristics of the eligible participants are summarized in Table 1.
studies are summarized in Tables 1 and 2. Period of inclusion ranged from 2000 to 2016. Nine studies detected HA in stroma or tumor by immunohistochemical staining, while one study tested HA in tumor by immunoradiometric analysis, and two studies tested HA in plasma by enzyme linked immunosorbent assay. OS was reported in 6 articles, while DFS or RFS was reported only in 2 articles. Besides, in discovery and validation cohort, Peng et al examined the HA level in plasma of breast cancer patients for different model adjustment (age or clinical pathological factors),[33] thus we got four HR estimates for OS and PFS respectively in one article. HR was reported directly in 4 articles and estimated indirectly in the other 3 articles.

3.4. Publication bias and sensitivity analysis

Figure 6, no significant results could be in publication bias among the included studies. Meanwhile, almost symmetrically (Fig. 5). The both OS and DFS/RFS/PFS studies, the funnel plots were showed.

The relationship between HA level and some clinical characteristics of patients (Fig. 4).

3.3. Correlation between HA level and clinicopathologic parameters

The relationship between HA level and some clinical characteristics was evaluated through the ORs derived from each available study, including tumor grade, tumor size, lymph node metastasis, distant metastases, ER, and PR status (Table 4). There were no significant relationships between high HA level and clinicopathologic parameters. However, a tendency shows that lymph node metastasis (OR = 1.55, 95% CI: 0.96–2.49, P = .07) and tumor grade (OR = 2.10, 95% CI: 0.89–4.96, P = .089) were statistically significant in the correlation study of HA level on the clinical characteristics of patients (Fig. 4).

3.2. Correlation between HA and survival outcome with subgroup analysis

According to the heterogeneity of 12 data with OS result (I^2 = 66.3%, P = .001), we chose a random model to examine the pooled HR and its corresponding 95% CI. The result showed there was a significant association between a high HA level and poor OS (HR = 1.86, 95% CI: 1.28–2.71, P = .001) (Fig. 2A). Similarly, the heterogeneity of ten studies with DFS/RFS/PFS results was statistically significant (I^2 = 66.4%, P = .002), and the random-effects model was used to calculate the pooled HR and its 95% CI, which was significantly different (HR = 1.63, 95% CI: 1.14–2.33, P = .007) (Fig. 2B). The result showed that higher HA level in breast cancer was related to a worse DFS/RFS/PFS.

To determine whether the sample type has an effect on the prognostic role of HA in breast cancer, we performed the subgroup analysis for OS by the sample type (Fig. 3). After divided into two subgroups, the heterogeneity for each group was solved (I^2 = 0%, P = .582 for stroma group and I^2 = 0%, P = .700 for plasma group). Moreover, a high HA level in stroma (HR = 1.63, 95% CI: 1.06–2.51, P = .025) and plasma (HR = 3.26, 95% CI: 2.25–4.73, P < .001) both significantly predicted poor OS. Details are shown in Table 3. However, the HR of HA in plasma is higher than that of HA in stroma.

4. Discussion

Because of high mortality and poor prognosis, breast cancer is the leading cancer in females. As mentioned previously, significantly increased levels of HA in carcinomas is considered as a biomarker for some solid tumor types, such as bladder, prostate, breast, lung, and colon.[14–20] As a major glycosaminoglycan in ECM, HA can modulate tumor microenvironment to promote the malignant phenotype, which may be explained by the biological characteristics of HA. Besides, some clinical studies have indicated that HA enhances the capacity invasion, motility, and EMT of breast cancer cell, by triggering various signaling pathways and through upregulation of collagen-degrading enzymes expression.[24–30]

Recently, a series of quantitative studies reported the prognostic role of HA in various cancers. Sun et al demonstrated that high-level HA in stroma predicts unfavorable recurrence-free survival (HR = 2.712, 95% CI:1.323–5.560, P = .006) and OS (HR = 1.736, 95% CI:1.050–2.871, P = .032) in HPV-negative oral cavity cancer.[52] In colorectal cancer, Llaneza et al also reported that high tumor cytosolic HA levels indicates shorter relapse-free survival and OS periods (both P < .05).[53] Consistency with Llaneza’s result, Kobel’s report also showed the pooled RR of OS 5.06 (95%CI: 1.18–21.57, P = .028.[54]

However, insignificant or opposite results were also reported...
in some studies. Florian et al found that presence of HA alone is not of prognostic importance in pancreatic ductal adenocarcinoma.\[55]\] Corte et al showed that high HA intratumoral levels were significantly associated with longer RFS in the subgroup of patients with ductal histological type tumors \((P = .01)\).\[34]\] Overall, the relationship between HA and prognosis in breast cancer patients remains conflicting and inconsistent. Therefore, we conducted this meta-analysis to comprehensively assess the relationship between HA and survival in breast cancer patients based on 7 articles.

Our comprehensive meta-analysis from 7 articles with a cohort of 2664 patients showed the high HA is associated with poor survival (both OS and DFS/RFS/PFS) in breast cancer patients. As known, breast tumor is a heterogeneous cancer and its prognosis is mainly affected by molecular subtype and tumor’s status.\[56]\] Therefore, we selected a random-effect model to minimize the influence of these differences, which may confuse the result of meta-analysis. Simultaneously, subgroup analyses were conducted according to the three sites where HA come from (tumor, stroma, and plasma). The heterogeneity diminished significantly.
in the stroma and plasma subgroup but not in tumor subgroup. Due to limited number of clinicopathologic parameters studied, though there was no significant correlation between HA level and tumor size, distant metastases, ER, and PR status, a tendency shows that tumor grade and lymph node metastasis were significant in the association study of HA level and the clinical characteristics of patients. The latter is consistent with Kettunen’s result, which showed that the positive correlations of peritumor/tumor apparent diffusion coefficient ratio with lymph node positivity and high HA content.

Although we are the first to conduct a meta-analysis on the predictive effect of HA for survival in breast cancer, our study still has some limitations. First, the obvious heterogeneity of the enrolled study in the OS group is caused by the different sample sites, methods, the cut-off values of HA and the follow-up duration. Second, although no significant publication bias was detected in the meta-analysis, all the studies being retrospective and usually single center with small sample size cohorts, which was relatively insufficient to determine the conclusion. Third, several HRs which were calculated from the survival curve may be slightly erroneous. Moreover, although some papers from developing countries were researched about relationship between HA and breast cancer diagnosis or metastasis, the patients included in this study are only from developed countries. Finally, some cases included in the pooled analyses of OS and DFS/RFS/FFS were analyzed by univariate analysis, which is less reliable than multivariate analysis because composite factors are considered in multivariate analysis. Moreover, different covariates were adjusted in each study, thus leading bias to the pooled results. Despite these limitations, this meta-analysis has demonstrated the correlation between HA level and breast cancer.

In addition, more research is needed to actually exploit the prognostic value of HA. First, only one article detected the HA levels in plasma, while others used tumor tissue or stroma samples. It is well known that plasma detection can conveniently provide timely information about host responses. Therefore, researchers should evaluate the prognostic value of HA in plasma for breast cancer. Second, the lack of a gold standard for HA threshold limits, its application to routine clinical management. Therefore, the HA cut-off value should be clearly defined based on the global population.

In conclusion, although large-scale and multicenter prospective studies are needed to confirm these findings, our meta-analysis provides statistical evidence that the high level of HA can predict unfavorable breast cancer outcomes. The HA could be a new prognostic biomarker helpful for the selection of individual therapeutic strategy for breast cancer patients.

**Author contributions**

All authors have read and approved the final version of the manuscript.

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