Systematic Review and Meta-Analysis

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Prognostic value of SUV_{max} in breast cancer and comparative analyses of molecular subtypes

A systematic review and meta-analysis

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Abstract

Background: To assess the prognostic capability of the maximum standardized uptake values (SUV_{max}) measured in the primary tumor and axillary lymph nodes (ALNs) by pretreatment fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography and analyze outcomes according to the molecular breast cancer subtypes.

Methods: The databases were systematically searched using keywords for breast cancer, positron emission tomography/computed tomography, and SUV_{max}; the extracted studies reported at least 1 form of survival data, event-free survival (EFS) and overall survival. Comparative analyses of the pooled hazard ratios (HRs) for EFS and overall survival were performed to assess their correlations with SUV_{max}. The pooled HR was estimated using random-effects model according to the results of heterogeneity.

Results: Thirteen eligible studies comprising 3040 patients with breast cancer were included. The pooled HRs of high SUV_{max} in the primary tumor and ALN were 3.01 (95% CI 1.83–4.97, $P < .00001$; $I2 = 82\%$) and 3.72 (95% CI 1.15–12.01; $I2 = 92\%$; $P = .03$), respectively. Patients with higher SUV_{max} demonstrated a poorer survival prognosis. Furthermore, comparative analyses according to the molecular subtypes demonstrated that the SUV_{max} in the primary tumor or ALN can be a predictive parameter in patients with the luminal subtype disease. Subtype analysis results indicated a significant association of the luminal group, with a HR of 2.65 (95% CI 1.31–5.37; $I2 = 27\%$; $P = .007$).

Conclusions: SUV_{max} from pretreatment is a significant prognostic factor for EFS in patients with breast cancer. Despite several limitations, correlation with molecular subtype (luminal type) was demonstrated. Further large-scale studies are required to investigate the precise prognostic capability of SUV_{max}.

Abbreviations: ^{18}F-FDG PET/CT = fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, ALN = axillary lymph node, EFS = event-free survival, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratios, MFS = metastasis-free survival, OS = overall survival, SUV_{max} = maximum standardized uptake values.

Keywords: breast cancer, meta-analysis, prognostic value, SUVmax

1. Introduction

Breast cancer, the second leading cause of cancer-related death and accounting for the highest number of solid cancers in women, is a heterogeneous malignancy that exhibits various patterns of progression, outcomes, and treatment responses.[1]

Although early diagnosis and effective treatment improved the survival rate, approximately 10% to 15% of locoregional recurrence was still reported after treatment.[2] As breast cancer is a very heterogeneous disease, accurate prediction of its prognosis is especially important in light of the variability of the disease

Editor: Wenwen Zhang.

All analyses were based on previously published studies; therefore, no ethical approval and patient consent were required.

There are currently no funding sources.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Lee Mi, Jung YJ, Kim DI, Lee S, Jung CS, Kang SK, Pak K, Kim SJ, Kim HY. Prognostic value of SUV_{max} in breast cancer and comparative analyses of molecular subtypes: A systematic review and meta-analysis. Medicine 2021;100:31(e26745).

Received: 18 January 2021 / Received in final form: 11 June 2021 / Accepted: 29 June 2021

http://dx.doi.org/10.1097/MD.0000000000026745

characteristics before developing a treatment plan. It is affected by variable factors including tumor size, nuclear grade, axillary lymph node (ALN) involvement, and hormone receptor status. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), among various imaging modalities, has also been reported to be valuable in the initial staging, restaging, evaluating treatment response, and predicting the prognosis of breast cancer.[3,4]

Among the various values determined using ^{18}F-FDG PET/CT, the most widely used parameter is the maximum standardized uptake value (SUV_{max}) that quantifies the rate of metabolic uptake of glucose by the tumor cells. Several recent systematic reviews and meta-analyses have found that the SUV_{max} of ^{18}F-FDG could serve as a prognostic factor in various malignant solid tumors.[5–8] Like other one else, several studies have reported the correlation of higher SUV_{max} of the primary tumor with poorer prognostic behavior even in breast cancer.[9,10]

Tumor size and the number of involved lymph nodes are well-established prognostic factors in breast cancers;[11,12] similarly, the molecular subtypes also defined according to the estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) statuses are precise and useful prognostic indicators.[13,14]

However, the prognostic value of SUV_{max} according to each molecular subtype of breast cancer is controversial, and no consensus exists of its predictive capability.[15,16]

Therefore, we conducted a meta-analysis to assess the prognostic value of SUV_{max} and its correlation with molecular cancer subtype in patients with breast cancer.

2. Materials and methods

2.1. Study selection and data extraction

PubMed, EMBASE, and Medline databases were searched for original articles (until March 2021). The search strategy involved using the following terms "breast cancer," "carcinoma," "positron emission tomography," "PET/CT," "fluorine-18-fluorodeoxyglucose," "^{18}F-FDG," "standardized uptake value," or "SUVmax." All searches were limited to human studies and English-language publications. The inclusion criteria for the studies were pretreatment, including surgery; use of 18F-FDG PET/CT as an initial imaging modality; measurement of SUV_{max} of the metabolic level of the primary lesions or ALN; and studies with at least one form of survival data, such as overall survival (OS), disease-free survival, event-free survival (EFS), progression-free survival, or metastasis-free survival. Reviews, abstracts, and editorial materials were excluded, and duplicate data were also removed. Authors independently performed the initial screening by reviewing the titles and abstracts according to the inclusion and exclusion criteria. Additionally, the following data were extracted from the publications: first author, year of publication, country of origin, study period, follow-up duration, age of patients, number of patients, and study design. Discrepancies were resolved by consensus.

2.2. Statistical analysis

The primary outcome was EFS, defined as the time from initiation of therapy until recurrence or progression. Data regarding disease-free survival, relapse-free survival, and recurrence or progression-free survival were obtained as the primary outcomes and were redefined as EFS.[6,7] If available, the secondary endpoint was OS. The OS was defined as the time from therapy initiation until death irrespective of the cause.[5,7]. To reconstruct the estimated HR on the survival data, survival data were extracted using the methodology recommended by Parmar et al.[17] The effects of SUV_{max} on survival outcomes were estimated by pooling the HR effect size and 95% CI data. The pooled HR was estimated using random-effects model according to the results of heterogeneity. An HR >1 indicated worse prognosis in patients with high SUV_{max}, and an HR <1 was indicative of better prognosis. *P* values of the log-rank test, 95% CI, number of events, and number at risk provided by the authors were extracted to estimate the HR indirectly using ReviewManager (RevMan, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration). The level of heterogeneity across individual studies was assessed using χ^2 test and I^2 statistics as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org). *P* values <.05 were considered statistically significant except for heterogeneity. The publication bias was evaluated by funnel plots.

2.3. Ethics approval

All analyses were based on previously published studies; therefore, no ethical approval and patient consent were required.

3. Results

3.1. Study characteristics

The searching of the electronic databases initially led to the identification of 2955 articles. After the exclusion of animal studies (n=256), non-English articles (n=146), conference abstracts, letter, editorial (n=1228), and 1271 studies that did not meet the inclusion criteria based on the title and abstract, the full text of 54 articles was reviewed; finally, 13 eligible studies with 3040 patients were included in our meta-analysis[18–30] (Fig. 1). Visual inspection of the funnel plot did not identify substantial asymmetry.

Among the 13 studies, 12 studies evaluated the prognostic value of SUV_{max} measured in the primary tumor,[18,20–30] 4 studies evaluated the SUV_{max} for ALN,[20,22,24,30] and 2 articles included values for both primary lesion and ALN.[24,26]

In each study, patients were divided into 2 groups based on the SUV_{max} threshold (<optimal cutoff value and >optimal cutoff value). Different studies had different optimal cutoff values determined using different methodologies. In all the 13 studies, the optimal cutoff values were determined using the area under the receiver operating characteristic curve. The cutoff SUV_{max} in the primary tumor ranged between 2.9 and 11.1, and those of SUV_{max} in ALN ranged from 1.7 to 2.8 (Table 1).

The EFS was analyzed based on 11 studies with SUV_{max} from the primary tumor.[18,20–24,26–30] The pooled HR for adverse events was 3.01 (95% CI 1.83–4.97, $P<.00001$; $I^2=82\%$) (Fig. 2A).

In subgroup analysis, in 9 studies using PET/CT, the pooled HR for adverse events was 3.11 (95% CI 1.74–5.58). In 2 studies using PET, the pooled HR for adverse events was 2.78 (95% CI 1.62–4.77).

Among the 13 studies, 3 studies additionally included the result of the OS rate, such that the 3 studies with SUV_{max} from the

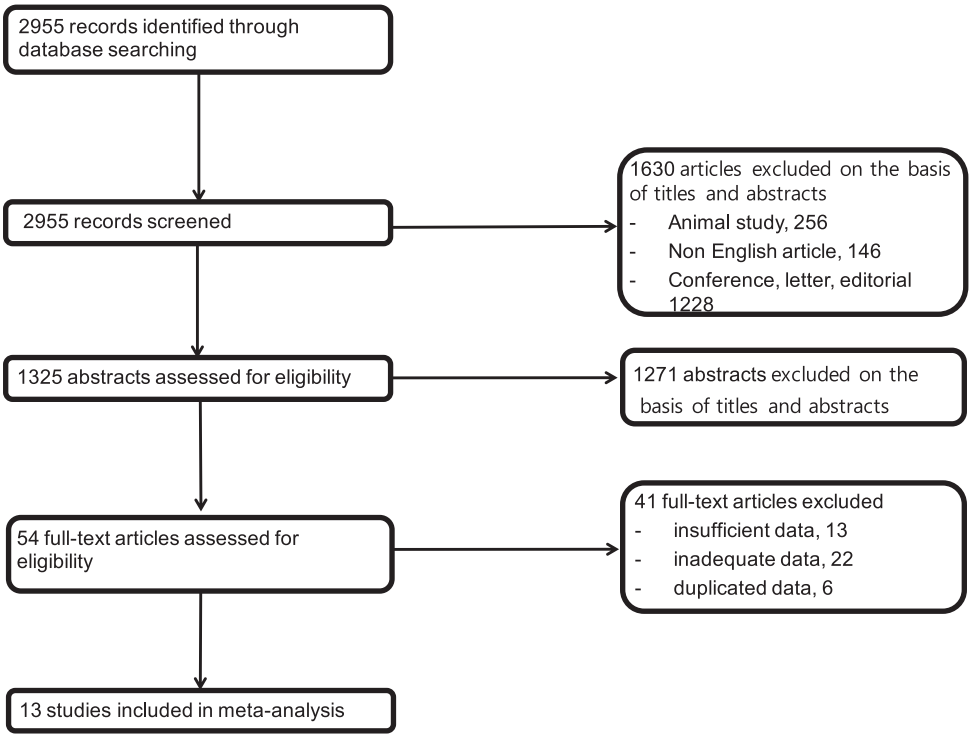

Figure 1. Flowchart for the identification of eligible studies.

primary tumor were included in the second analysis of OS.[26,29,30] The pooled HR was 3.43 (1.80–6.52; I2 = 24%; $P = .0002$) (Fig. 2B).

In an analysis of the prognostic value of high SUV_{max} from the primary tumor, primary tumors with a high SUV_{max} were found to be associated with progression and recurrence and had poor OS rates. Similarly, the prognostic value of high SUV_{max} from ALN was also analyzed based on 4 studies.[20,22,23,24] In an analysis of the prognostic value of high SUV_{max} from ALN, a similar predictive value of SUV_{max} as that of the primary tumor was observed. Additionally, ALN with a high SUV_{max} was associated with progression and recurrence. The pooled HR for adverse events, including death, was 3.72 (95% CI 1.15–12.01; I2 = 92%; $P = .03$), which was also significant (Fig. 3).

3.2. Molecular biological subtype comparative analyses

Of the 13 eligible studies, the results of 4 were extracted according to each molecular subtype. Using the same method, the subgroup comparative analyses according to molecular subtype were obtained. Three studies[19,22,25] were included for analyzing the prognostic value of SUV_{max} in patients with luminal subtype (ER+/HER−) and 2 studies each were used in the assessments of triple-negative (ER−/HER−) and[23,25] HER2(+) subtype (ER−/

Table 1

Studies included in meta-analysis.

Author	Year	Country	Study design	No. of patients	Histology	Staging (AJCC 7th)	Endpoints	Scanner	Lesion	FDG uptake time(min)	Image reconstruction method	Cutoff value	Determination of cutoff values
Jung et al	2017	Korea	R	131	IDC+ILC+other	I, II, III	EFS	PET/CT	Primary tumor	60	Maximization algorithm	5.5	AUC
Higuchi et al	2017	Japan	R	387	IDC+ILC+other	I, II, III	EFS	PET/CT	Primary tumor	60		3.585	AUC
Kitajima et al	2016	Japan	R	196	IDC+ILC+other	I, II, III	EFS	PET/CT	Primary tumor/node	60		2.9/1.7	AUC
Jo et al	2015	Korea	R	508	IDC	I, II, III	EFS	PET/CT	Primary tumor	60	Iterative reconstruction	5.95	AUC
Vicente et al	2015	Spain	R	198	IDC+ILC	II,III	EFS/OS	PET/CT	Primary tumor/node	60	Iterative reconstruction	6.05/2.25	AUC
Yue et al	2015	USA	R	79	IDC+ILC	I–IV	EFS	PET/CT	Primary tumor	60	Iterative reconstruction	3.5	AUC
Kim et al	2015	Korea	R	153	IDC	II, III	EFS	PET/CT	Primary tumor/node	60	Iterative reconstruction algorithm	11.1/2.2	AUC
Aogi et al	2015	Japan	R	262	IDC+ILC	I,II,III	EFS/OS	PET/CT	Primary tumor	60–90	Iterative reconstruction	6.0	AUC
Baba et al	2014	Japan	R	79	IDC+ILC+other	I,II,III	EFS/OS	PET	Primary tumor	60		4.16	AUC
Cochet et al	2014	France	R	142	IDC+ILC	II,III,IV	EFS	PET/CT	Primary tumor	60		5.7	AUC
Ahn et al	2013	Korea	R	496	IDC+ILC+other	I,II,III	EFS	PET	Primary tumor	60	Iterative transmission algorithm	4	AUC
Kadoya et al	2013	Japan	R	344	IDC+ILC+other	I,II,III	EFS	PET/CT	Primary tumor	60–90	Iterative algorithm	3	AUC
Song et al	2012	Korea	R	65	IDC	II,III	EFS	PET/CT	Primary tumor/node	60	Maximum iterative reconstruction algorithm	6.9/2.8	AUC

IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, R = retrospective.

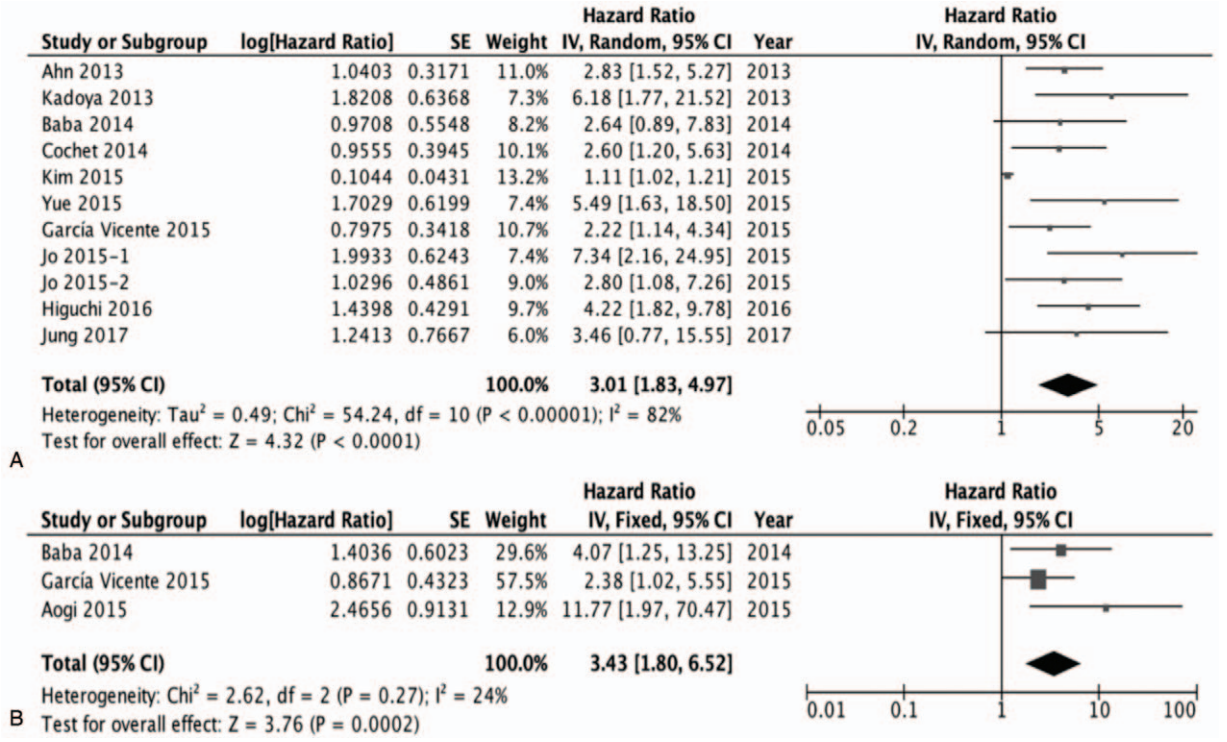

Figure 2. A, The prognostic value of SUVmax (primary tumor) for EFS. B, The prognostic value of SUVmax (primary tumor) for OS. EFS = event-free survival, OS = overall survival, SUV_{max} = maximum standardized uptake values.

HER+) tumors.[19,25] SUV_{max} could serve as a prognostic factor for EFS in patients with the luminal subtype of breast cancer. The results of subtype comparative analyses indicated a significant association of the luminal subgroup of tumors, with a HR of 2.65 (95% CI 1.31–5.37; I2 = 27%; $P = .007$) (Fig. 4A).

Given the availability of OS data from 2 studies,[22,25] we were able to analyze the prognostic value of SUV_{max} for OS. However, the pooled HR for OS was 2.63 (95% CI 0.14–49.77; I2 = 81%; $P = .52$), which was not significant (Fig. 4B).

No significant association was found in the assessment of patients with triple-negative subtype and patients with HER2(+) subtype (triple negative; HR [95% CI 0.33–13.26; I2 = 80%; $P = 0.43$], HER2(+); HR 2.44 [95% CI 0.82–7.24; I2 = 0%; $P = .11$]) (Figs. 5 and 6).

4. Discussion

The Precision Medicine Initiative, launched in January 2015, requires more accurate diagnoses and prognoses, utilizing optimal treatment patterns, reducing the risk of treatments and side effects, and ensuring less cost.[32] To improve treatment outcome, effective personalized therapeutic strategies are required for more aggressive treatments, especially in patients with more aggressive diseases.[31] Therefore, before operation or for adjuvant treatment, stratifying the risk of patients for recurrence or progression is very essential. ^{18}F-FDG PET/CT is a clinically useful noninvasive imaging modality for the diagnosis of metastases or preoperative initial staging of breast cancers.[33,34] Recently, as a prognostic factor in breast cancer, the use of the

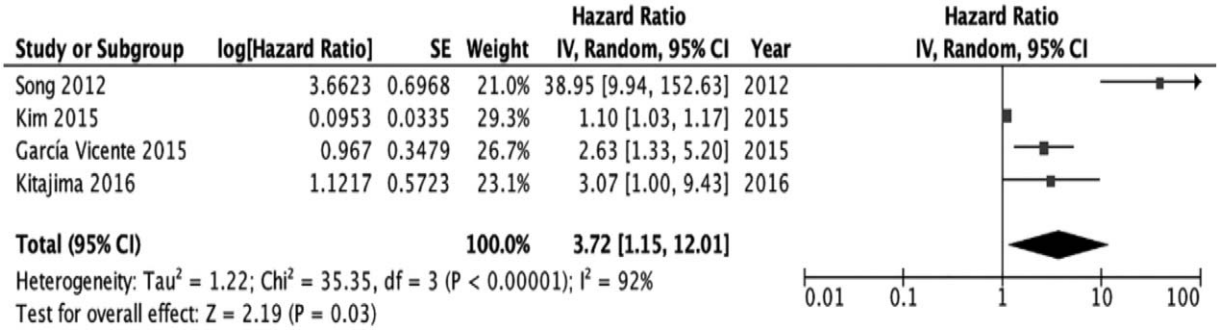

Figure 3. The prognostic value of SUVmax (axillary lymph node) for EFS. EFS = event-free survival, SUV_{max} = maximum standardized uptake values.

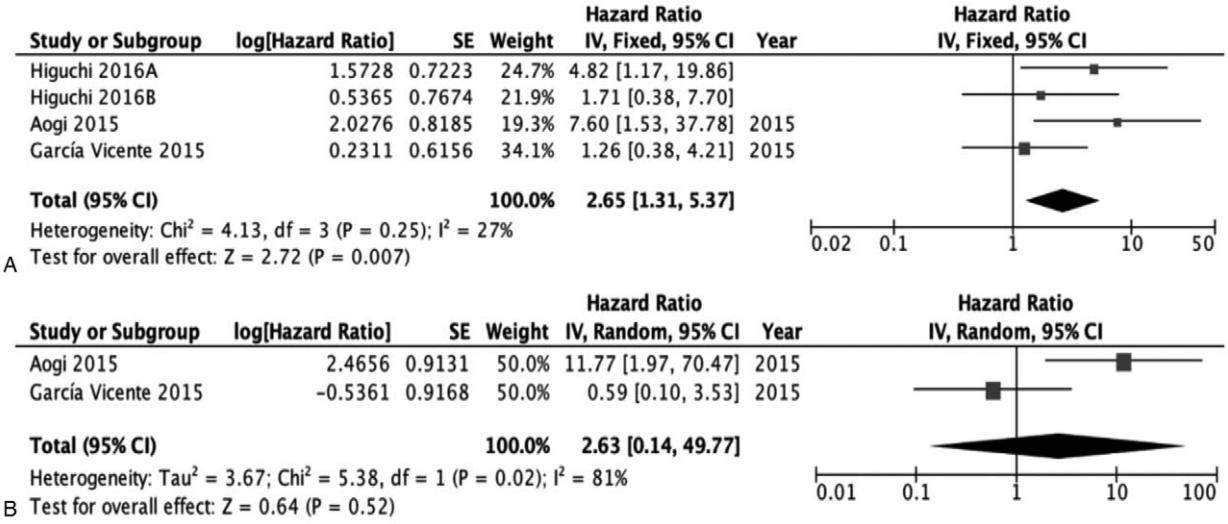

Figure 4. In luminal subtype. A, The prognostic value of SUVmax (primary tumor) for EFS. B, The prognostic value of SUVmax (primary tumor) for OS. EFS = event-free survival, SUV_{max} = maximum standardized uptake values.

SUV_{max} value as the most widely used parameter in the clinical settings has increased.[35] The SUV_{max} of primary lesion has significant prognostic value for EFS or OS in different cancers, such as cervical, lung, and esophageal cancers.[5–8]

Additionally, several reports have suggested that tumors with high SUV_{max} are associated with poor prognosis in patients with breast cancer.[10,21,29] Increasing SUV_{max} was related to the aggressive behavior of the cancer, and patients with high SUV_{max} might have a higher risk of recurrence or progression.[36] Therefore, in patients with high SUV_{max}, more aggressive treatment is considerably effective and benefits EFS or OS. In different cancers, tumor size and the number of involved lymph nodes are well-established significant prognostic factors as these are closely associated with the progression and the development of distant metastases.[12] Especially, tumor size and ALN involvement in breast cancer are also significant predictors of relapse and in determining cancer staging.[37,38] Furthermore, defining molecular subtypes according to ER and HER2 statuses should be considered to stratify the risks of recurrence or death in patients with breast cancer, following which adjuvant treatments are determined based on each subtype.[13,35]

To investigate not only the prognostic value of SUV_{max} in patients with breast cancer but also conduct a comparative assessment according to each molecular subtype, this meta-analysis reanalyzed approximately 3040 patients from 13 studies by calculating the pooled HR for EFS and/or OS in patients with high SUV_{max} compared with those with low SUV_{max}. Patients with a high SUV_{max} of the primary tumor or ALN demonstrated a higher risk of adverse events than those with a low SUV_{max}. Hence, in terms of biological subtypes, only the luminal subtype group with a high SUV_{max} demonstrated a higher risk of adverse events. The luminal subtype group with high SUV_{max} might, thus, have a higher risk of recurrence or progression than the low SUV_{max} group.

However, a significant predictive value for EFS in patients with other biological subtypes was not identified. This may have been due to the insufficient statistical power, as there were only 2 or 3 studies available for the comparative study of each subtype, comprising a relatively small number of patients. Furthermore, the limited sample size and significant heterogeneity could also result in low statistical efficiency. Further research is required to investigate whether the correlation between each biological subtype and SUV_{max} of the primary tumor or ALN can be of effective prognostic value in patients with breast cancer. However, there were certain advantages to our meta-analysis. HR was used to calculate the prognostic value in this meta-analysis. HR is the most appropriate measure for prognosis because the odds ratio is measured at a single point in time; therefore, it is not recommended as a surrogate method for analyzing time-to-event outcomes.[39] However, this meta-

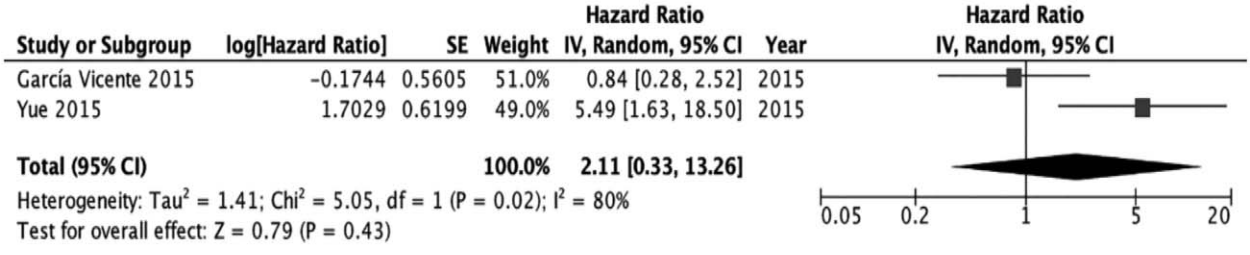

Figure 5. The prognostic value of SUVmax (primary tumor) for EFS in triple negative subtype.

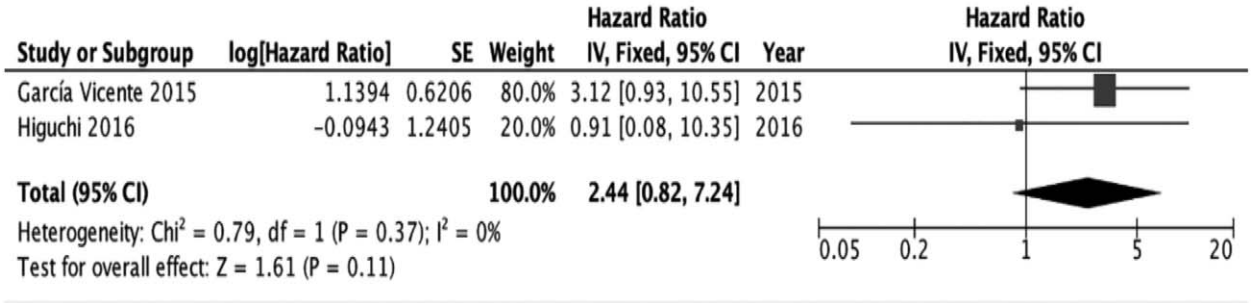

Figure 6. The prognostic value of SUVmax (primary tumor) for EFS in HER2(+) subtype. EFS = event-free survival, HER2 = human epidermal growth factor receptor 2, SUV_{max} = maximum standardized uptake values.

analysis had several limitations also. First, the included articles were restricted to the English language only; thus, the potential effect of language bias should be considered. Second, a potential publication bias in the studies cannot be clearly excluded even though funnel plots showed no clear evidence. Lastly, all included studies were retrospective in nature, and so selection bias could not be excluded.

5. Conclusion

Our meta-analysis indicated that high SUV_{max} of the primary lesion or ALN could predict a higher risk of adverse events in the patients. In patients with the luminal subtype, there is a correlation between the prognostic value of SUV_{max} for EFS and molecular subtypes. The pretreatment SUV_{max} is a significant prognostic factor in patients with breast cancer because a high SUV_{max} can be considered a high risk for treatment failure; therefore, patients with high SUV_{max} may benefit from a more aggressive treatment. Therefore, pretreatment SUV_{max} in patients with breast cancer could serve as a prognostic factor for planning an effective treatment strategy. Given the limitations due to sample size and heterogeneity, further research, including large-scale prospective studies, is required to investigate more precise prognostic capabilities of SUV_{max}.

Acknowledgments

The authors thank Editage (www.editage.co.kr) for English language editing

Author contributions

The first author, Moon il Lee planed and wrote this manuscript
Other co-authors played a role in the data organization and modulation of this article
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Methodology: Kyoungjune Pak.
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Supervision: Kyoungjune Pak, Seong Jang Kim, Hyun Yul Kim.
Validation: Seungju Lee, Chang Shin Jung.
Writing – original draft: Moon il Lee.
Writing – review & editing: Hyun Yul Kim.

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