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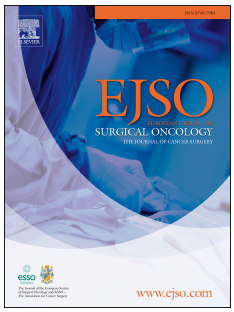

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Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: a systematic review and an exploratory meta-analysis

Alessia Nottegar[a], Nicola Veronese[b], Maheswari Senthil[c], Rudi M Roumen[d], Brendon Stubbs[e], Audrey H Choi[c], Nicole Verheuvel[f], Marco Solmi[g], Antonio Pea[h], Paola Capelli[a], Matteo Fassan[b] Giuseppe Sergi[b], Enzo Manzato[b], Marco Maruzzo[i], Fabio Bagante[h], Mehmet Koç[j], Mehmet A Eryilmaz[k], Emilio Bria[l], Luisa Carbognin[l], Franco Bonetti[a], Mattia Barbareschi[m], Claudio Luchini[a,m,n]

[a] Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy

[b] Department of Medicine, DIMED, University of Padua, Padua, Italy

[c] Department of Surgery, Loma Linda University, Loma Linda, California

[d] Department of Medical Oncology,School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, The Netherlands

[e] Health Service and Population Research Department, King's College London, De Crespigny Park, London, UK

[f] Department of Surgery, Máxima Medical Center, Veldhoven, The Netherlands

[g] Department of Neuroscience, University of Padua, Padua, Italy

[h] Department of Surgery, University and Hospital trust of Verona, Verona, Italy

[i] Medical Oncology Unit, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy

[j] Necmettin Erbakan University, Meram Medical School Department of Radiation Oncology, Konya, Turkey

[k] Health Science University, Konya Training and Educational Hospital, Department of General Surgery, Konya, Turkey

[l] Medical Oncology, University and Hospital Trust of Verona, Verona, Italy

[m] Department of Pathology, Santa Chiara Hospital, Trento, Italy

[n] ARC-NET Research Center, University and Hospital Trust of Verona, Verona, Italy

Corresponding Author:

Dr. **Claudio Luchini**, MD

Department of Diagnostics and Public Health

University and Hospital Trust of Verona

Piazzale Scuro, 10

37134 Verona, ITALY

Phone: 0039.045.812.4842

Fax: 0039.045.812.7136

Email: claudio.luchini@katamail.com ; claudio.luchini@univr.it

ABSTRACT

Invasive breast cancer is the most common malignancy in women. Its most common site of metastasis is represented by the lymph nodes of axilla, and the sentinel lymph node (SLN) is the first station of nodal metastasis. Axillary SLN biopsy accurately predicts axillary lymph node status and has been accepted as standard of care for nodal staging in breast cancer. To date, the morphologic aspects of SLN metastasis have not been considered by the oncologic staging system. Extranodal extension (ENE) of nodal metastasis, defined as extension of neoplastic cells through the nodal capsule into the peri-nodal adipose tissue, has recently emerged as an important prognostic factor in several types of malignancies. It has also been considered as a possible predictor of non-sentinel node tumor burden in SLN-positive breast cancer patients. We sought out to clarify the prognostic role of ENE in SLN-positive breast cancer patients in terms of overall and disease-free survival by conducting a systematic review and meta-analysis. Among 172 screened articles, 5 were eligible for the meta-analysis; they globally include 624 patients (163 ENE+ and 461 ENE-) with a median follow-up of 58 months. ENE was associated with a higher risk of both mortality (RR= 2.51; 95% CI: 1.66-3.79, $p<0.0001$, $I^2=0\%$) and recurrence of disease (RR=2.07, 95%CI: 1.38-3.10, $p<0.0001$, $I^2=0\%$). These findings recommend the consideration of ENE from the gross sampling to the histopathological evaluation, in perspectives to be validated and included in the oncologic staging.

INTRODUCTION

Invasive breast cancer is the most common malignancy in women, representing 23% of all cancers in woman globally and 27% in affluent countries. It is more than twice as common as cancer at any other site [1]. The most common site of metastasis of breast cancer is represented by the lymph nodes of axilla, and the sentinel lymph node (SLN) is the first station of nodal metastasis [1-3].

Axillary SLN biopsy was introduced in the management of patients affected by T1 and T2 breast cancer and has become the standard care for these patients, being an accurate method in predicting other axillary lymph nodes status [2-3]. The probability of non-SLN metastases in patients with SLN free of metastases is less than 5%. For this reason, such patients can safely avoid axillary lymph node dissection and the associated morbidity [2-6]. Patients with positive SLN were traditionally treated with axillary lymph node dissection [5-6]. However, about 40-60% of these patients have no other metastatic axillary lymph nodes, suggesting that even this group is heterogeneous.

Several factors have been studied as potential predictors of the status of axillary lymph nodes in patients with positive SLN, and some of them have not demonstrated a prognostic value. For example, the presence of isolated tumor cells in the SLN does not adversely impact disease free- and overall-survival, and, according to the Tumor, Nodes, Metastasis (TNM) staging system, isolated tumor cells are designated and treated as pN0(i+) [7]. At the same time, extranodal extension (ENE) has recently emerged as an important prognostic factor in several types of malignancies [8-11]. It is the extension of neoplastic cells through the nodal capsule into the peri-nodal

adipose tissue (**Figure 1**). In positive SLN, ENE has been indicated as a possible predictor of non-SLN tumor burden in breast cancer, but it is yet unclear if ENE in SLN has a significant prognostic impact [12].

In order to study in depth the prognostic role of ENE in positive SLN of breast cancer patients, we conducted a systematic review and meta-analysis of all the studies that have investigated the most important prognostic indicators, including overall survival (OS), disease-free survival (DFS) and cancer-specific survival, in patients with (ENE+) versus without (ENE-) ENE in SLN.

MATERIALS AND METHODS

This systematic review adhered to the MOOSE guidelines [13] and PRISMA statement [14], following a predetermined but unpublished protocol.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they satisfy the following criteria: 1) diagnosis of breast cancer, 2) prospective, observational cohort studies, 3) contained a comparison of prognostic factors between ENE+ vs. ENE- for SLN, 4) contained data about mortality or recurrence of disease, 5) were published in a peer review journal or published abstract. Exclusion criteria were: 1) no presence of cancer, 2) no data about prognostic parameters in the title/abstract, 3) comparison between ENE+ vs. no lymph nodes metastases (N0), 4) diagnosis of non-epithelial malignancies (i.e.: lymphomas), 5) ENE+ for lymph nodes other than SLN, and 6) in vitro or animal studies. We considered articles written in any language.

Data sources and literature search strategy

Two investigators (C.L., N.V.) independently searched PubMed and SCOPUS until 09/30/2015. The search terms used in PubMed included combinations of the following keywords: (extracapsular OR pericapsular OR extranodal OR perilymphatic OR perinodal OR “extra capsular” OR “peri-capsular” OR “extra nodal” OR “peri lymphatic” OR “peri nodal” OR “extra-capsular” OR “peri-capsular” OR “extra-nodal” OR “peri-lymphatic” OR “peri-nodal”) AND (sentinel) AND (mortality OR mortalities OR fatality OR fatalities OR death* OR survival OR recurrence OR

prognosis OR "hazard ratio" OR HR OR "relative risk" OR RR OR prognosis OR progression). A similar search was conducted in SCOPUS. We considered also the reference lists of all included articles.

Study selection

Following the searches as outlined above, after removal of duplicates, two reviewers (A.N.. and M.S.) screened independently titles and abstracts of all potentially eligible articles. The two authors applied the criteria of eligibility, considered the full texts and a final list of included articles was reached through consensus with a third independent author (N.V.).

Data extraction

Two authors were involved in the data extraction from a predetermined Excel database. Particularly, one author (A.N.) extracted data from the included articles and a second independent author (C.L.) validated the data. For each article, we extracted information about authors, year of publication, country, exclusion criteria, tumor size and grading, age, ENE definition, and duration of mean follow-up. In case of missing data, authors were contacted at least 4 times in one month by e-mail.

Outcomes

The main outcomes were number of deaths independent from all the causes (all-cause mortality), number of deaths due to cancer (cancer-specific mortality), and number of recurrences (disease free survival) during follow-up period by ENE status.

Assessment of study quality

The Newcastle-Ottawa Scale (NOS) [15] was used to evaluate study quality. The NOS provides an assessment of the methodological quality of non-randomized trials and its content validity and reliability have already been established [13]. Included studies are judged on 8 items across three key areas: selection of the participants, comparability of the participants, and outcomes. One author (C.L.) completed the NOS and each study receives an overall score for methodological quality of up to 9 points.

Data synthesis and statistical analysis

All analyses were conducted using Comprehensive Meta-Analysis (CMA) 3.

In our primary analyses, pooled risk ratios (RRs) and 95% CIs of all-cause mortality and recurrences of disease between ENE+ vs. ENE- were calculated using DerSimonian-Laird random-effects models [16]. Since data about hazard ratios (HRs) adjusted for the maximum number of covariates were available only for two studies, we summarized these findings descriptively.

Heterogeneity across studies was assessed by the I^2 metric and chi square statistics [17]. Since no outcome from the meta-analysis was heterogeneous, (i.e. $I^2 \geq 50\%$ and/or a p-value <0.05 [15]), no meta-regression analysis was performed.

Finally, we investigated publication bias for our primary meta-analysis with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau [18] and Egger bias test [19].

RESULTS

Search Results

Altogether, 172 non-duplicated articles were identified through the literature search. After excluding 160 articles based on title/abstract review, 12 articles were retrieved for full text review and, following the application of the inclusion criteria (exclusion of 7 studies: doubled cohort = 1 study, no data on SLN = 3 studies, reviews = 2 studies, no control group = 1 study), 5 unique articles resulted as eligible for this meta-analysis [20-24] (**Supplementary Figure 1**).

Study and Patient Characteristics

The studies were conducted in Europe (2 studies) [21,24], Asia (2 studies) [22,23] and North America (1 study) [20]. Altogether, 624 patients (163 ENE+ and 461 ENE-) were followed-up for a median of 58 months (range: 20-73). The median NOS score was 6 points (range: 5-9) (**Supplementary Tables 1-2).**

All studies (except one) defined ENE using a classical definition, i.e. as the presence of full-thickness lymph node capsular invasion or with the extension of tumor cells into peri-nodal adipose tissue. Only one study [23] reported salient demographic data by ENE status limiting the applicability to these findings to other studies.

Risk Ratios on Overall survival and Disease-Free Survival

Pooling data from 4 studies reporting data on overall survival [20,21,23,24], 22.5% with ENE+ for sentinel lymph node were dead vs. 9.6% with ENE-, leading to a significant increased risk of mortality (RR= 2.51; 95% CI: 1.66-3.79, $p<0.0001$, $I^2=0\%$) (**Table 1; Figure 2A**). ENE+ was further associated to a significant higher

risk of recurrence of disease (5 studies) [20-24]; RR=2.07, 95%CI: 1.38-3.10, p<0.0001, I^2=0%) (**Table 1; Figure 2B**).

For both outcomes, publication bias was unlikely as indicated by the Egger's test (bias=1.47; p=0.33) and Begg–Mazumdar test (Kendall's tau = 0.17, p =0.73).

No studies reported data on cancer-specific mortality.

Descriptive findings

Two studies [20,23] also reported results of analyses regarding the association between ENE and prognostic factors by ENE status, adjusted for potential confounders (**Supplementary Table 3**). Regarding OS, taking in account 5 possible confounders, Choi et al. [20] reported an increased risk of mortality for those having ENE+ at the baseline (OR=8.16, 95%CI: 1.72-38.67), while Shigematsu et al. [23] reported a HR of 3.70 (95%CI: 1.08-12.72) considering 9 possible confounders. Similar findings emerged for DFS, since Choi et al. [20] reported an OR of 5.48 (95%CI: 1.23-24.45, p=0.03) for those ENE+ and Shigematsu et al. [23] a HR of 4.50 (95%CI: 1.77-11.47). Due to intrinsic diversities in such indexes (OR is not comparable to HR), a meta-analysis summarizing them was not possible.

DISCUSSION

In this study we analyzed 5 observational studies involving 624 SLN positive breast cancer patients. Of them, 163 presented extra-nodal extension, while 461 showed only intra-nodal metastasis. Our findings demonstrate that ENE was associated with a higher risk of mortality (RR= 2.51; 95% CI: 1.66-3.79, p<0.0001, I^2=0%) and recurrence of disease (RR=2.07, 95%CI: 1.38-3.10, p<0.0001, I^2=0%). Both of the analyses were homogenous and without any evidence of publication bias.

Previous studies have clearly demonstrated that ENE in axillary SLN metastasis is an important predictor of non-sentinel lymph node tumor burden. Cserni in 2001 and Stitzenberg et al. in 2003 found that ENE of the SLN metastasis is a strong predictor of non-SLN involvement also in multivariate analysis, and that in such cases completion of axillary lymph nodes dissection may be important [25,26]. These results were further corroborated with a meta-analysis by van la Parra *et al.* [12]. In this meta-analysis 8 factors including ENE in the SLN were identified as predictive of non-SLN tumor burden. With the size of SLN metastasis (>2 mm vs. ≤2 mm), ENE emerged as one of the most clinically relevant indexes to predict further non-SLN metastasis [12]. Despite a well-defined role of ENE in the SLN metastasis in the prediction of non-SLN involvement, its role as a prognostic factor in terms of overall mortality has not been established until now. Our findings show that the presence of ENE in SLN is strongly associated with a poor prognosis in terms of overall survival and disease free survival. Although there were not a sufficient number of studies reporting the HR, adjusted for potential confounders, to perform a meta-analysis, the present findings based on RR appear sufficiently robust to generate the hypothesis of a significant prognostic role of ENE in SLN positive breast cancer.

There are some important implications that can be derived from this study. The first regards the need of a standard definition of ENE, since this parameter, should be considered by future staging systems and also be reported in the final pathology report. Four out of 5 studies assessed ENE classically, i.e. as the extension of metastatic cells through the nodal capsule into the perinodal adipose tissue [20,21,23,24]. The study by Fujii et al. [22] considered ENE as the extra-capsular growth of tumor cells, the invasion of perinodal fat or the extranodal location of tumor cells, extending in this way the classic definition. Using this definition, also free tumor deposits in the adipose tissue surrounding the SLN could be included in our meta-analysis, introducing a possible bias. However, this study represents a minor proportion (7.4%) of the total number of ENE+ patients to significantly affect our findings, and as discussed before no heterogeneity was present.

This point further reiterates the importance of adopting a standard definition of ENE. We suggest define as true ENE the one that is demonstrated histologically and characterized by a structural rupture of the lymph node capsule by the metastasis. Neoplastic emboli as well as free tumor cell deposits in adipose tissue and metastasis in the marginal sinus should not be considered as true ENE. Notably, the presence of tumor cells in the adipose tissue is recognized as associated to a poor prognosis in colorectal cancer. In this type of cancer, this parameter has been recognized by the TNM staging system designing for it a specific subcategory of N group, named N1c [7,9]. Furthermore, ENE has also been taken into account in the last staging systems of squamous cell carcinoma of the vulva, playing an important, adverse prognostic role [11]. In the 5th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, ENE was considered also for breast cancer, in a specific subcategory, named pN1biii, but this was removed from the 6th edition of the same

staging system [27,28]. It is possible that some evidences against its usefulness in the staging system and also problems in the standardization of ENE definition, with a difficult inter-observer agreement, affected the consideration of its prognostic importance. However, on the basis of the present results, we suggest to reconsider the possible prognostic role of ENE, also in perspectives to be validated by future clinical trials.

Recently, the Z0011 trial demonstrated no difference in loco-regional recurrence and overall survival in breast cancer patients with a positive SLN randomized to axillary lymph node dissection or no further surgery, changing the surgical management of T1 and T2 breast cancer patients with metastatic involvement of the axilla limited to the SLN [29]. However, it is important recognizing patients who meet the Z0011 strict criteria of inclusion but at the same time have a certain high-risk characteristics, as for example the presence of ENE. The incidence of ENE in SLN ranges from 24% to 40% [20,26,30]. Due to its high incidence, due to its association with non-SLN metastasis, as even highlighted by Cserni and Stitzenberg et al. in a multivariate analysis [25,26], and by van la Parra et al. in a meta-analsysis [12], and also due to the results of this meta-analysis, it seems advisable to offer completion of the axillary lymph node dissection, rather than not.

When considering the therapeutic in other cancer types (e.g. pancreatic ductal adenocarcinoma), ENE+ patients seem to benefit from adjuvant chemo-radiation, but not from chemotherapy alone [8,31]. This aspect should be further addressed by future studies, and could address peculiar therapeutic approaches if confirmed also for breast cancers as well. Noticeably, even after the Z0011 trial, some radiation oncologists still recommend additional radiation fields in selected cases such as ENE+ in SLN [20,32].

Whilst the results of this meta-analysis are clear and reliable, we have also to consider some limitations of our paper. The first is the small number of studies; however, the significant number of patients presented in these studies (mean number: 125 patients/study) as well as their high NOS quality index and the absence of a high heterogeneity of the results ensure a certain grade of reliability. Furthermore, data about other co-morbidities (like cardio-vascular diseases) were not reported by the primary studies, but it's known that they play an important role in the prognosis also of patients with cancer. Moreover, it lacks a comprehensive landscape of the clinical data of the patients, since only one study [23] reported this kind of information (tumor size, nodal status, tumor grading) by ENE status, limiting general considerations about these topics. Therefore, future research should try and disentangle the role of co-morbidities on the observed results and should report more complete clinical data. Another limitation of this meta-analysis derived from the lack of data from multivariate analyses: only two studies [20,23] presented data from multivariate models, both significant, but not comparable with a meta-analysis (odds ratios in a study [20] vs hazard ratios in the other [23]). Future studies should consider also this important point, reporting data on ENE from multivariate analysis.

Concluding, the present data indicate that ENE in SLN positive breast cancer seems to be strongly associated with a poorer prognosis in breast cancer. Its consideration becomes thus essential from the gross sampling to the histopathological evaluation and the oncologic staging. In spite of the recently developed techniques (e.g. DNA sequencing) which allow integrating the pathological report with a complete molecular characterization of the tumor in the so called "next-generation histopathological analysis" [33,34], all the prognostic roles of the pure morphologic features and of the histologic aspects, including ENE, should be clarified.

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The funding source has not influenced the study design, the collection, analysis and interpretation of data, the writing of the manuscript and the decision to submit and where submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

The Authors declare no conflict of interests.

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FIGURE CAPTIONS

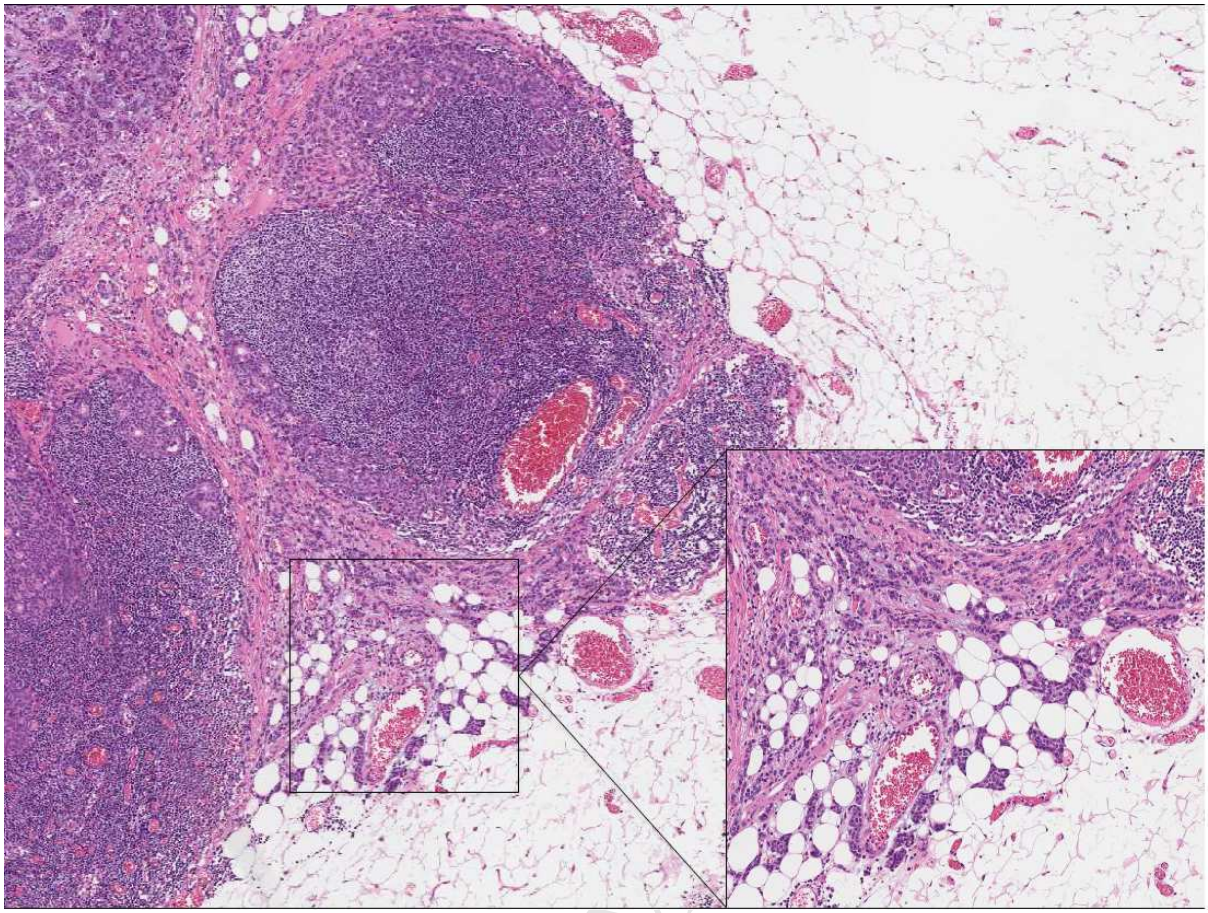
Figure 1. A classical example of extra-nodal extension of nodal metastasis is here shown. The metastatic tumor is a breast carcinoma of non-special type. Note the rupture of nodal capsule and the invasion by the metastatic cells of the peri-nodal adipose tissue. (Original magnification: 4x lymph node, 10x detail in the box).

Figure 2. Forrest plots for Relative Risk for Overall Survival (A) and Disease-Free Survival (B)

Table 1. Pooled risk ratio estimates for overall and disease free survival according to presence or not of extra-nodal extension.

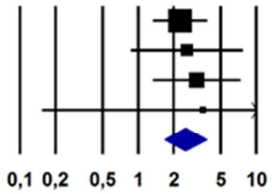
Parameter	N Studies	N of Events* in ENE+	N of ENE+	N of Events* in ENE-	N of ENE-	Risk Ratio (95% CI)	P-Value	Heterogeneity
Overall survival	4	34	151	41	423	**2.51 (1.66-3.79)**	**<0.0001**	$Tau^2 = 0.00$; $Chi^2 = 0.45$, df =3 (P=0.93); $I^2 = 0\%$
Disease free survival	5	36	163	51	461	**2.07 (1.38-3.10)**	**<0.0001**	$Tau^2 = 0.00$; $Chi^2 = 1.87$, df = 4 (P =0.76); $I^2 = 0\%$

Abbreviations: ENE: extra-nodal extension. *Events stand for death for overall survival and relapse for disease-free survival.



A

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Choi, 2015	2,263	1,332	3,845	3,021	0,003
Shigematsu, 2015	2,587	0,870	7,695	1,709	0,087
Verheuvel, 2015	3,121	1,331	7,316	2,618	0,009
Erylmaz, 2011	3,529	0,154	81,106	0,789	0,430
	2,507	1,660	3,786	4,368	0,000



B

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Choi, 2015	1,611	0,856	3,033	1,478	0,139
Shigematsu, 2015	2,669	1,235	5,767	2,497	0,013
Verheuvel, 2015	1,878	0,780	4,522	1,406	0,160
Fujii, 2014	3,167	0,733	13,674	1,544	0,122
Erylmaz, 2011	5,882	0,303	114,284	1,171	0,242
	2,068	1,378	3,104	3,505	0,000