The relationship between time to surgery(TTS) after neoadjuvant chemotherapy (NAC)and survival in breast cancer patients: meta-analysis

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Abstract

PURPOSE: This meta-analysis aims to evaluate the impact of delaying surgery in operable breast tumor patients after neoadjuvant chemotherapy (NAC) on survival.

METHODS: An electronic literature retrieval was conducted on PubMed/Medline and EMBASE((between January 2000 and June 2020).The primary end point was overall survival(OS),secondary end points included disease-free survival (DFS) or recurrence-free survival (RFS).The HR with 95% confidence intervals were calculated using a random-effects or fixed-effects model.

RESULTS: The combined HR for OS was 1.52(95% CI 1.29-1.78; P = 0.000) by fixed-effects model.No statistically significant heterogeneity was found (P=0.114;I^2=39.8%).The pooled HR for RFS/DFS was 1.47 (95%CI: 1.27- 1.71,I^2=61.9%) by random-effects model, with significant heterogeneity.

CONCLUSION: Our meta-analysis revealed a significant adverse association between longer TTS after NAC and more inferior OS and RFS/DFS in patients with breast cancer.Clinicians and patients should minimize surgical delay after NAC as much as possible.

Background

Breast tumor is the most common malignancy in women today,and surgical treatment remains the primary treatment in most patients with breast cancer.Approximately 37–40% of breast cancer patients receive surgery[1]. Most patients begin adjuvant chemotherapy (AC) within a few weeks after breast surgery. However it is unknown whether delayed AC would result in poorer outcomes for breast cancer patients.Several studies have explored the appropriate timing of adjuvant chemotherapy for operative patients with breast cancer, and there is still no consensus on the optimal timing of postoperative AC for breast cancer patients. A systematic review and meta-analysis demonstrated that a longer waiting-time from surgery to AC would lead to worth outcomes, especially in triple-negative breast cancer (TNBC) patients[2].

A variety of clinical trials demonstrated that neoadjuvant chemotherapy (NAC) is a well-established treatment option for patients with locally advanced or inoperable breast tumors[3]. Furthermore,both early-stage and advanced breast tumors can benefit from NAC to increasing breast conservation rates[4]. While there have been few studies investigated the optimal operative time after NAC for patients with operable breast cancer.Our study aims to explore the impact of delaying surgery in operable breast tumor patients after NAC on survival.

Materials And Methods:

Data source: An electronic literature retrieval was conducted on PubMed/Medline and EMBASE((between January 2000 and June 2020).Search terms were used such as "timing to surgery” or "time to surgery" and "breast neoplasm" and "survival" published in English.

Selection criteria: The included literature needs to meet the following criteria: 1) All of the patients received preoperative NAC,the time interval from NAC to surgery was documented. 2) The relationship between the time from NAC to surgery and survival should be reported. 3) The primary end point was overall survival(OS),secondary end points included disease-free survival (DFS) or recurrence-free survival (RFS), 4) The hazard ratio (HR) with 95% confidence intervals (CIs) should be reported directly or sufficient data was provided to calculate them. To avoid publication bias, both the full-text and the summary of the meeting were included in our analysis.Patients would be excluded if they had received AC therapy, had stage IV disease, or had undergone mastectomy at an outside hospital.

Data extraction and quality assessment:

Two experienced authors ((S.Y.C and Z.X.G) independently extracted data from the included studies. The data extracted from the literature included: first author's name, publication year and country, population characteristics, waiting time,HR with corresponding 95%CI, and covariates in the fully adjusted model. RFS were treated as DFS in our analysis because the definition of RFS was similar to DFS[2]. Waiting time was defined the time interval from the end of preoperative NAC to initiation of surgery.Several studies had revealed that the earlier surgery was performed after preoperative NAC, the better outcome the patients would get. What's more, due to the impact on survival that caused by a too-short delay (i.e.one week) would so small that could not be observed, we used 4-weeks as cut-off in our meta-analysis.

We used the Newcastle–Ottawa Scale (NOS) criteria to assess the quality of all included studies[5]. Three studies showed high quality (≥8 points)[6], and all studies scored six points or more according to the NOS criteria, indicating the quality of all included studies was good[7]. Any disagreements on the quality assessment and data extraction would be resolved by consensus or consultation of a third party.

Statistical analysis:

We used the software Stata 15.0 to perform statistical analyses. And the I^2 statistic and the Q-test were used to assess statistical heterogeneity. When $P > 0.1$ and $I^2<50\%$, we used the fixed-effects model, once $P < 0.1$ and $I^2 >50\%$, the random-effects model was used[8]. Our analysis used funnel plots, the Begg and Egger tests to assess publication bias. Asymmetrical funnel plot and P-value of Egger's test (<0.05) suggested that there was publication bias in all studies[9,10]. For all the statistical analyses, $p<0.05$ was considered statistically significant.

Results

Data synthesis: A total of four hundred and five potentially relevant publications were found according to our initial search strategy, one hundred and sixteen publications from PubMed/Medline, two hundred and eighty-nine publications from Embase. There were three hundred and one publications after duplicate publications were removed; of these, we excluded two hundred and sixty-eight articles because the title or abstract did not meet the eligibility criteria. Eight systematic reviews, four studies on metastatic breast

cancer, and eleven non-neoadjuvant chemotherapy were further excluded. Eventually, nine articles[11–19] (eight studies) were identified as eligible for our analysis, including eight independent studies for OS, six studies for RFS, and two for DFS[14]. The flow chart of the literature search and study selection is shown in Fig. 1.

Study quality: The eligible studies were conducted in Australia, Saudi Arabia, Italy, Peru, the USA and Canada. The number of participants ranged from 58-1101 per study for 4521 patients across the ten studies. Detailed baseline characters of each eligible study were listed in table 1. Table 2 showed the HR results from each eligible study.

Data synthesis: The combined HR for OS was 1.52 (95% CI 1.29–1.78; P = 0.000) by fixed-effects model. No statistically significant heterogeneity was found (P = 0.114; I^2 = 39.8%), and this difference was statistically significant (Z = 4.31; p = 0.000), Fig. 2.

The pooled HR for RFS/DFS was 1.47 (95%CI: 1.27–1.71,I^2 = 61.9%,Fig. 3a) by random-effects model, with significant heterogeneity. When the study by T.L. Sutton et al. [12] which contributed substantial heterogeneity was excluded, low heterogeneity was found (P = 0.142, I^2 = 37,6%), the pooled HR was 1.41 (95% CI:1.22–1.64), the data was statistically significant (Z = 3.77, p = 0.000), Fig. 3b.

Sensitivity analysis was used to assess the root of heterogeneity. As shown in Fig. 4, the individual data set had no significant influence on the OS and RFS/DFS, demonstrating the reliability and stability of the results in our meta-analysis.

Asymmetrical funnel plot showed in Fig. 5a and P = 0.002 < 0.05 for Eggers test demonstrated that our studies existed publication bias for OS. Statistical tests also showed publication bias for RFS/DFS was found in our study (p < 0.05 for Eggers test and p = 0.003 for Beggs test), Fig. 5b. Then, trim-and-fill method was conducted to adjust funnel plots[20, 21]. Three missing studies were added in analysis of RFS/DFS and four studies in OS, Fig. 6. The recalculated results were still significant for RFS/DFS (HR = 1.33, 95% CI = 1.04–1.72; random-effects model; p < 0.01) and OS (HR = 1.38, 95%CI = 1.07–1.78, random-effects model; p < 0.01), indicating the conclusions in our meta-analysis were stable and reliable.

Discussion

The meta-analysis showed that TTS delays after NAC was positively connected with the risk of death in patients with operable breast cancer. The combined HR demonstrated that OS and RFS/DFS were significantly worse in patients with TTS > 4-weeks compared to patients with TTS < 4-weeks (HR = 1.49, P = 0.000, and HR = 1.40, P = 0.000). Therefore, it is responsible for considering that a 4-weeks delay in surgery after NAC is connected with an increase in the relative risk of death of approximately 49%, and 40% for RFS/DFS.

As shown in Fig. 4, the asymmetrical funnel plot revealed a publication bias in our meta-analysis. After adjusted by trim-and-fill method, the corrected results of RFS/DFS and OS were still statistically

significant (HR = 1.33; p < 0.01 and HR = 1.38, p < 0.01, respectively), indicating our results were robust and reliable.

Our meta-analysis had some limitations. Firstly, our finding was based totally on observational studies. We could not completely rule out the effect of confounding on our analysis. Therefore, the conclusion should be interpreted cautiously. Secondly, due to individual information not available, sub-analyses according to different features failed. Thirdly, different phenotypes of breast cancer would lead to uncertain prognosis;in part,survival is dependent upon breast cancer subtypes [22].However,because of insufficient information provided in the original studies, we did not further explore whether TTS delays after NAC had an impact on the prognosis of breast cancer patients with different hormone receptor and HER2 status. Despite these limitations, our meta-analysis still has crucial clinical directive significance. Physicians should minimize surgical delay after NAC for breast cancer patients when possible.

Conclusion

our meta-analysis revealed a significant adverse association between longer TTS after NAC and more inferior OS and RFS/DFS in patients with breast cancer. Clinicians and patients should minimize surgical delay after NAC as much as possible.

Declarations

Ethical approval and consent to participate :

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication:

Not applicable

Availability of data and materials:

Not applicable

Informed consent :

The study was approved by the local institutional review board, and the requirement for informed consent was waived because of the retrospective nature of this study.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

S.Y.C and Z.X.G collated data and did analyses. S.Y.C planned and performed analyses,and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Not applicable

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Tables

Table 1. Characteristics of studies selected for inclusion in this analysis.

References	Country	Median age，year	Menopausal status	Neoadjuvant chemotherapy treatment regimen	Stage	Sample size	Adjustment for covariates	Study qualiy	article type
Rachel A. Sanford et al. 2015	US	50 (24–83)	Mixed	Anthracycline- or taxane	I-III	1101	Multivariate, adjustmen; adjusted factors not reported	9	Full Text
Omarini, C et al. 2016	Italy	50 (26-80)	Mixed	NA	I-III	319	Multivariate adjustment; adjusted factors not reported	9	Full Text
Kausar Suleman et al. 2019	Saudi Arabia	44 （23-83）	Mixed	FEC(5-FU,epirubicin,andcyclophosphamide) and Taxotere ± Herceptin	II/III	611	Multivariate adjustment; adjusted factors not reported	8	Full Text
T.L. Sutton et al. 2020	US	NA	Mixed	NA	Mixed	463	Multivariate adjustment; adjusted factors not reported	6	abstract
LP Rebaza et al. 2019	Peru	49 （24-85）	Mixed	NA	II/III	583	Multivariate adjustment; adjusted factors not reported	6	abstract
Lai, V et al. 2015	Canada	NA	Mixed	NA	Mixed	347	Multivariate adjustment; adjusted factors not reported	6	abstract
Cinausero, M et al. 2018	Italy	NA	Mixed	NA	Mixed	683	Multivariate adjustment; adjusted factors not reported	6	abstract
F.Piacentini, et al. 2015	US	NA	Mixed	Anthra-taxanes/anthra/taxanes/CMF± Trastuzumab	I-III	295	Multivariate adjustment; adjusted factors not reported	6	abstract

Table 2. Outcomes reported in studies selected for inclusion in this analysis.

References	Stage	Hormone receptor-status	TTS	HR(95 % CIs)		
				OS	Recurrence-free survival (RFS)	DFS
Rachel A. Sanford et al. 2015	I-III	HR+ HER2+ TNBC	>4weeks VS. 0-4weeks	1.25(0.98-1.60)	1.25(0.98-1.59)	
Omarini, C et al. 2016	I-III	HR+ HER2+ TNBC	0-3weeks	1	1	
			>3weeks	3.1(1.1,8.6)	3.11(1.35,7.17)	
Kausar Suleman et al. 2019	II/III	NA	>4weeks VS. 0-4weeks	1.85(0.94-3.66)	1.48(0.96-2.28)	
T.L. Sutton et al. 2020	Mixed	NA	>6weeks VS. 0-6weeks	2.46（1.44-4.21）	4.614（2.14-9.97）	
LP Rebaza et al. 2019	II/III	32.7% luminalA 15.6% luminalB 24.4% Her2 27.3% TN	>4weeks VS. 0-4weeks	1.45（0.96-2.19）	1.38（0.97-1.98）	
Lai, V et al. 2015	Mixed	NA	>4weeks VS. 0-4weeks	1.82（0.94-3.51）		2.15（0.95-4.95）
Cinausero, M et al. 2018	Mixed	NA	>4weeks VS. 0-4weeks	1.37（0.93-2.03）	1.31（0.97-1.79）	
F.Piacentini, et al. 2015	I-III	LumA 18.3%, LumB/HER2-28.2% LumB/Her2+20.7% HER2+9.8% TNBC 21%	>5weeks VS. 0-5weeks	3.61(1.34-8.65)		3.77(1.42-9.95)

Figures

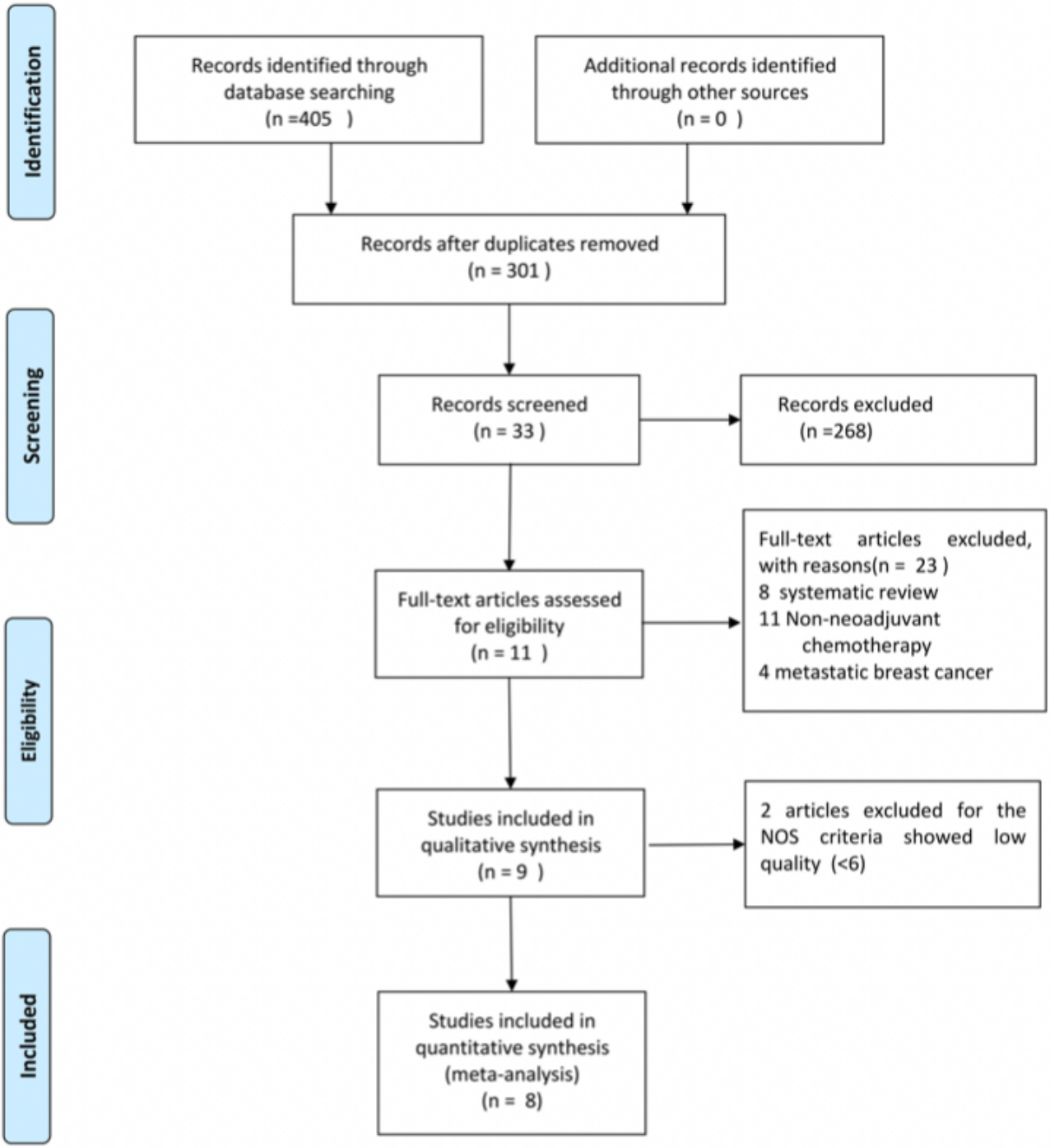


Figure 1

Flowchart of the study selection strategy

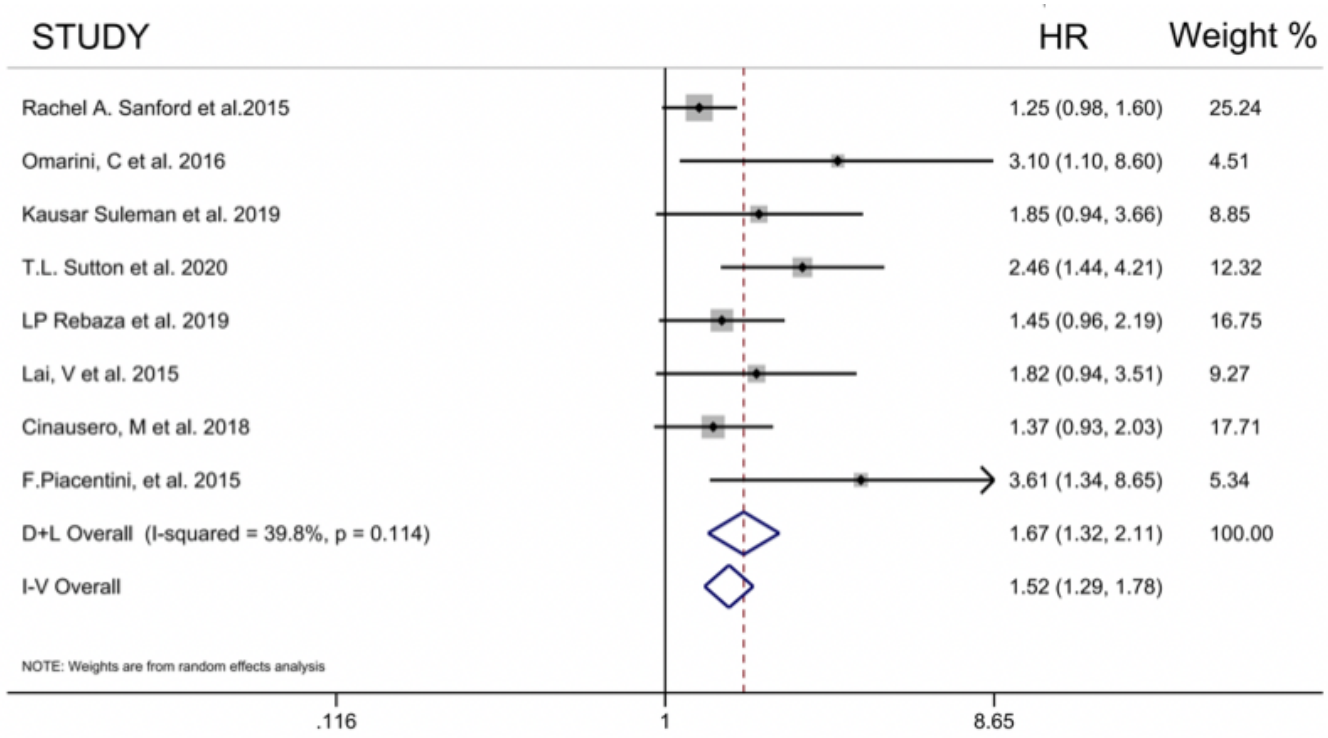


Figure 2

The association between 4-weeks surgical delay and OS.

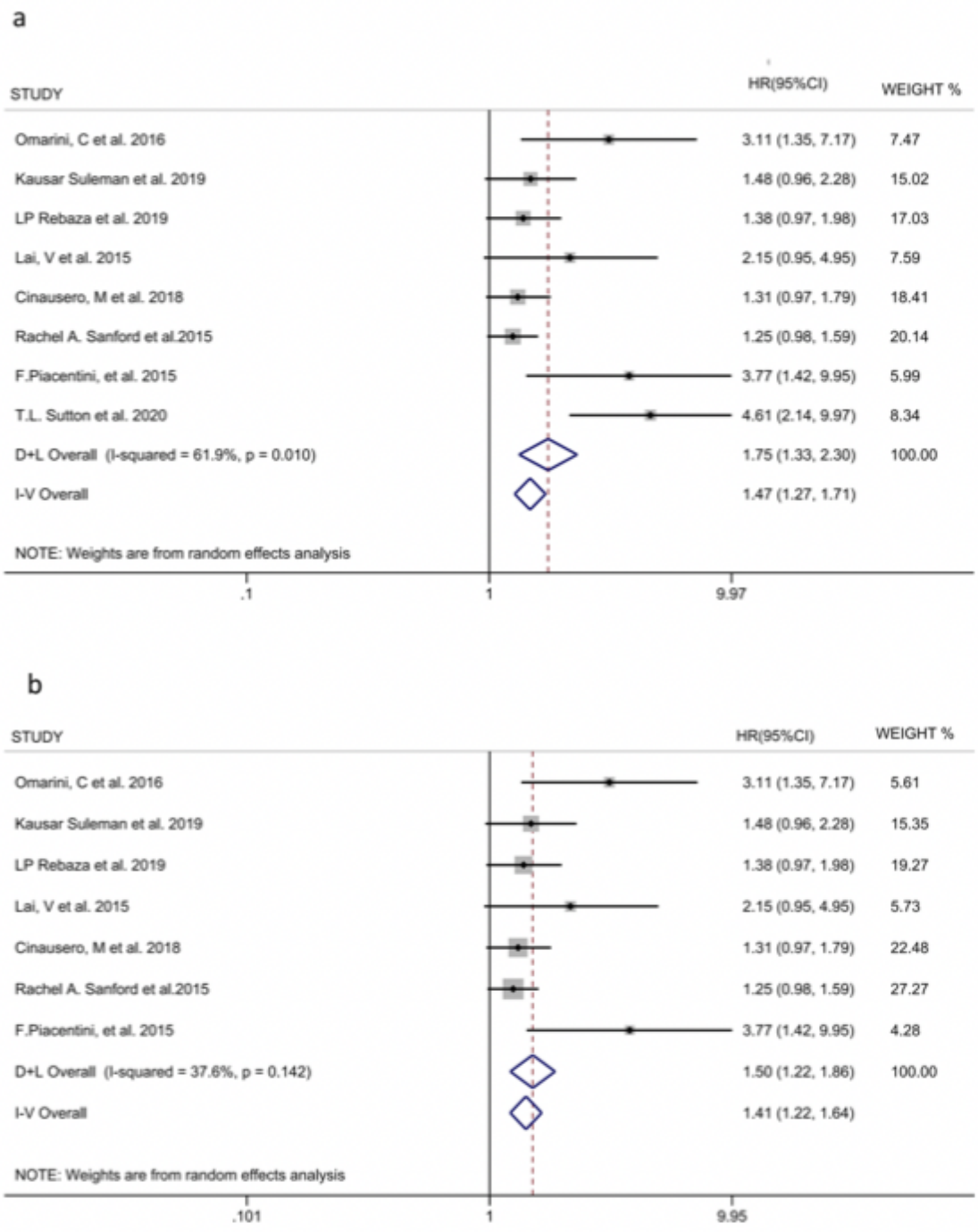
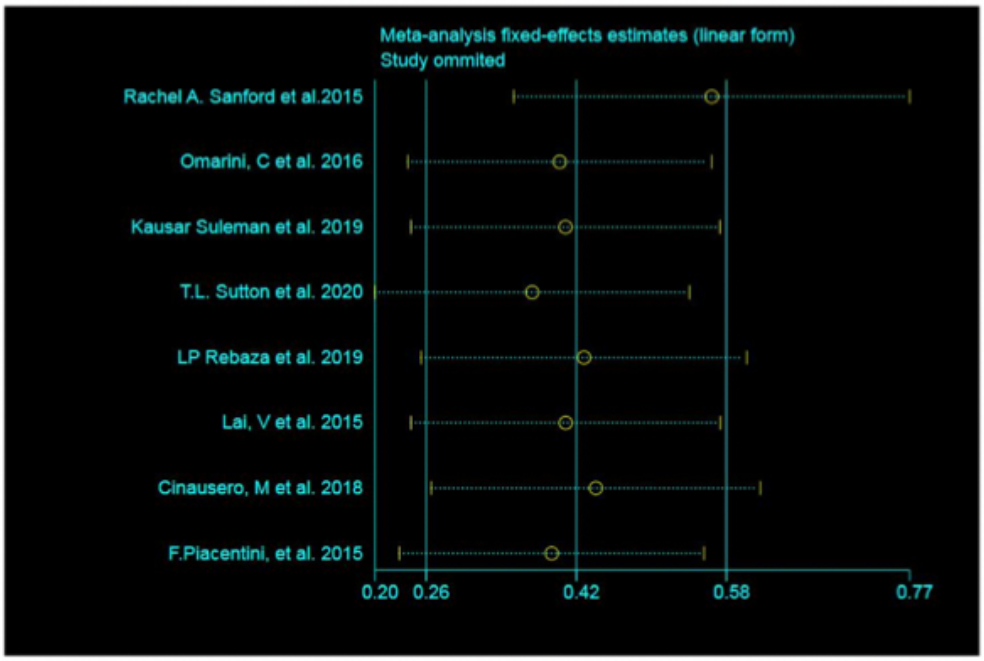


Figure 3

a: The association between 4-weeks surgical delay and RFS/DFS, b: The association between 4-weeks surgical delay and RFS/DFS after the study by T.L.Sutton was excluded.

a



b

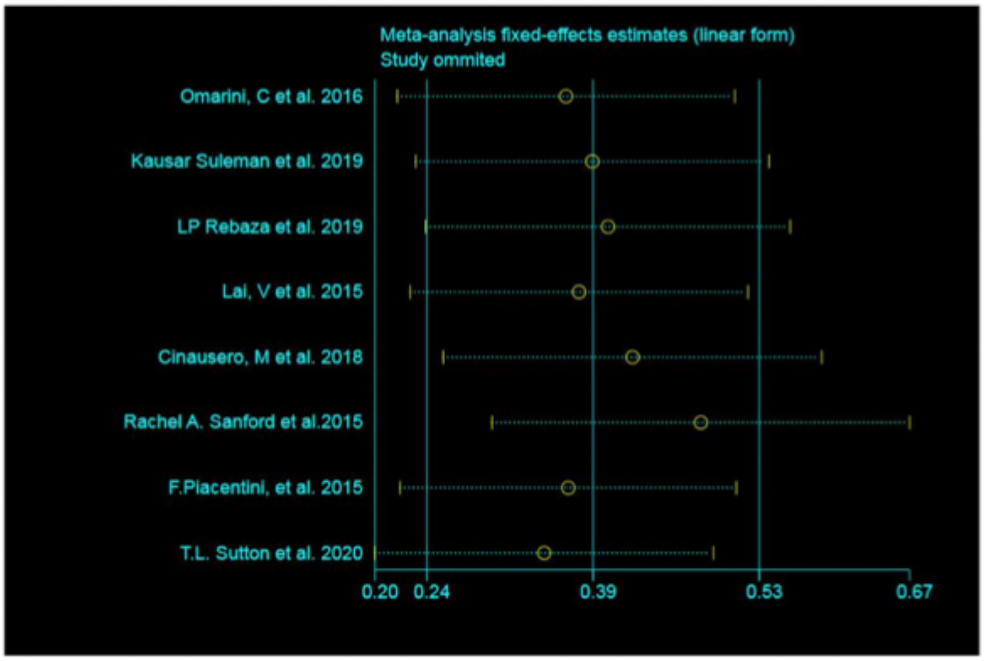


Figure 4

Sensitivity analyses for included studies concerning OS(a) and RFS/DFS(b).

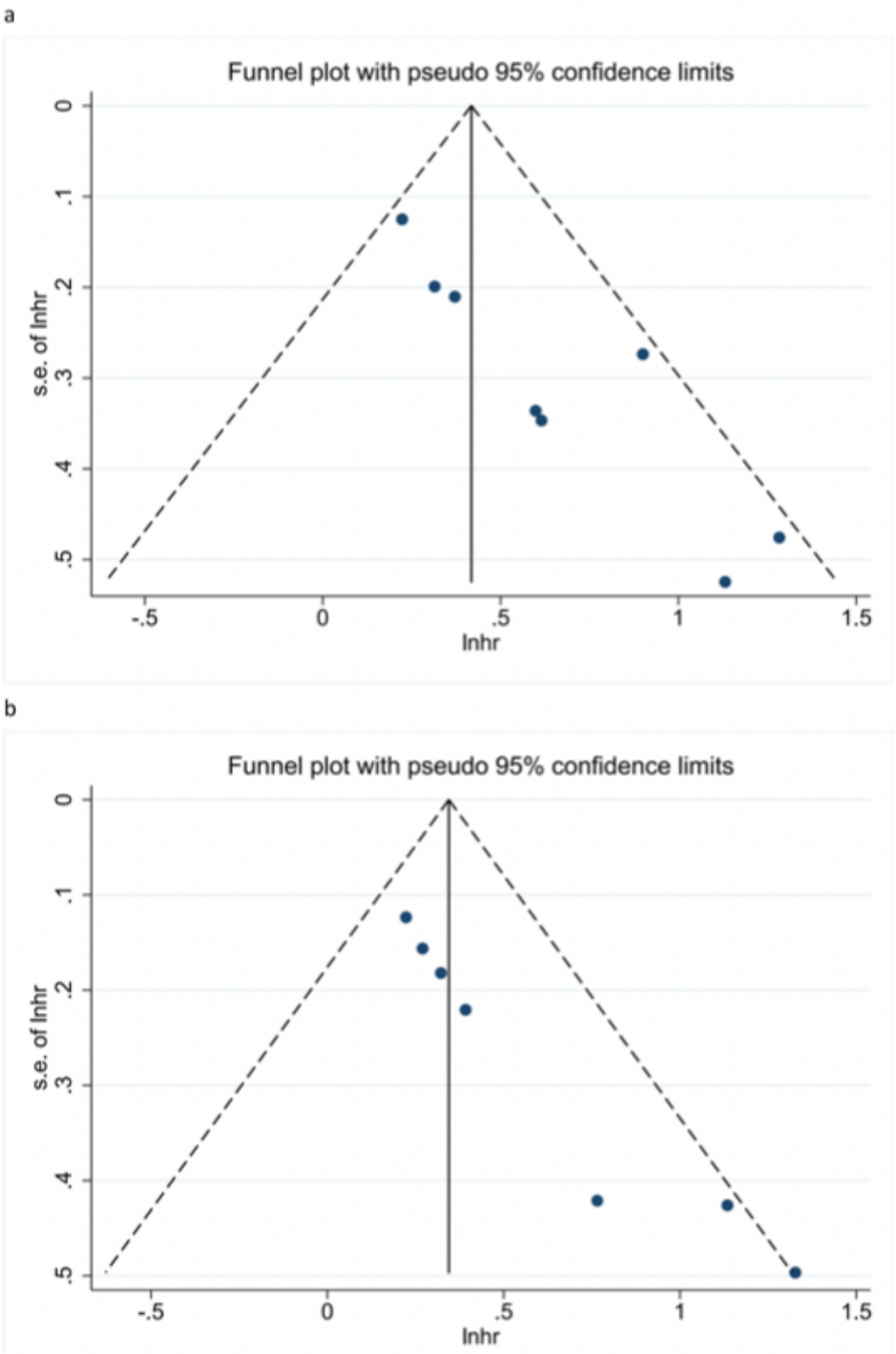
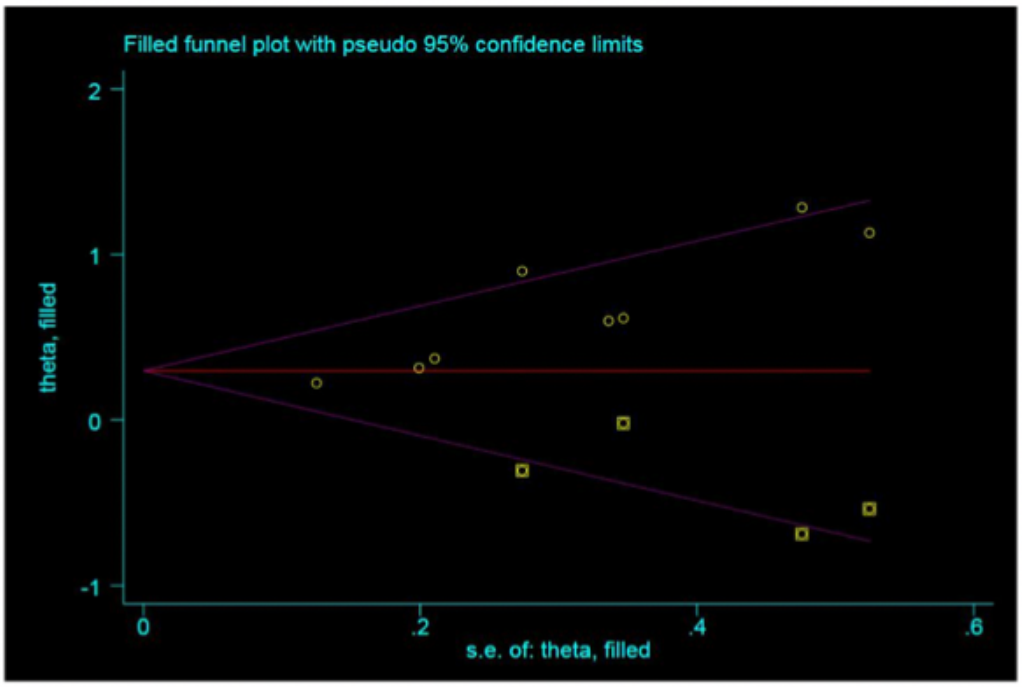


Figure 5

a.Funnel plot of the association between TTS and OS;b.Funnel plot of the association between TTS and RFS/DFS.

a



b

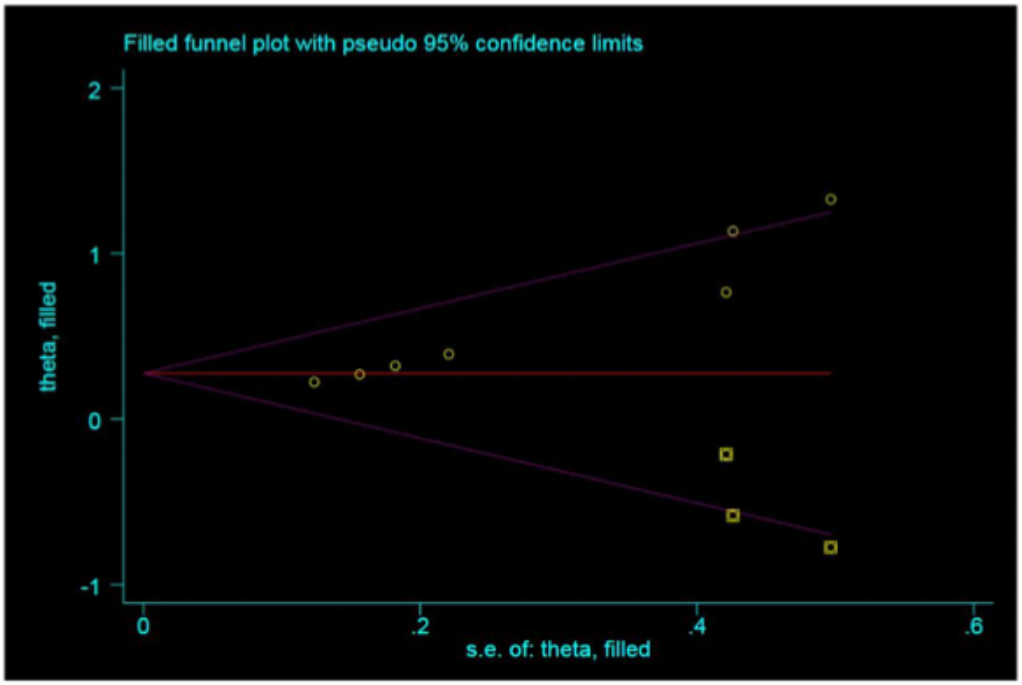


Figure 6

Publication bias test for the meta-analysis:Trim and fill test for OS (a) and RFS/DFS(b).