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Health-related Quality of Life in early breast cancer patients using trastuzumab: A systematic review and meta-analysis

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Introduction

In 2020, breast cancer is the most diagnosed cancer worldwide

Her2-positive breast cancer (Her2+) constitutes about 20% of the total breast cancer prevalence

The progressiveness of Her2 breast cancer encounters in the survivors' Health-related Quality of Life (HRQoL)

Patients irreversibly experienced physical and psychosocial syndrome, mental distress, and symptoms burden **as an impact of long-term treatment and disease progression**.

HRQoL, as the primary clinical outcome in Her2 breast cancer, has been taken into account to consider the treatment strategy for the advanced disease

Trastuzumab

A targeted therapy, remarkably effective in the HER2 overexpression of breast cancer

Has been proved in the clinical outcome improvement (DFS, OS, and iDFS in the management of Her2-early breast cancer

Review existed: 3 systematyic review, 8 meta-analysis → focusing on the efficacy and toxicity of Trastuzumab in early setting

Summarize the role of trastuzumab containing regimen in the HRQoL, including pooled analysis in the early setting

The systematic review and meta-analysis protocol has been registered in Prospero with the ID CRD42021259826.

Search strategy

- Pubmed, Embase, and Scopus. From March to May 2021.

The search terms

- Breast cancer, Trastuzumab, Quality of Life, and Quality-adjusted Life Years

Eligibility criteria

- Woman population with breast cancer in any stage who received trastuzumab in any cancer treatment regimens
- The studies providing HRQoL data which is reported using validated instruments
- The studies containing Quality-adjusted Life Years (QALYs) estimates
- The studies presenting original data; studies design for both Randomized Controlled trials and Cross-sectional
- Not restricted to the language and the year of published

Quality of Life and Quality Adjusted Life Years of Breast Cancer Patients using Trastuzum

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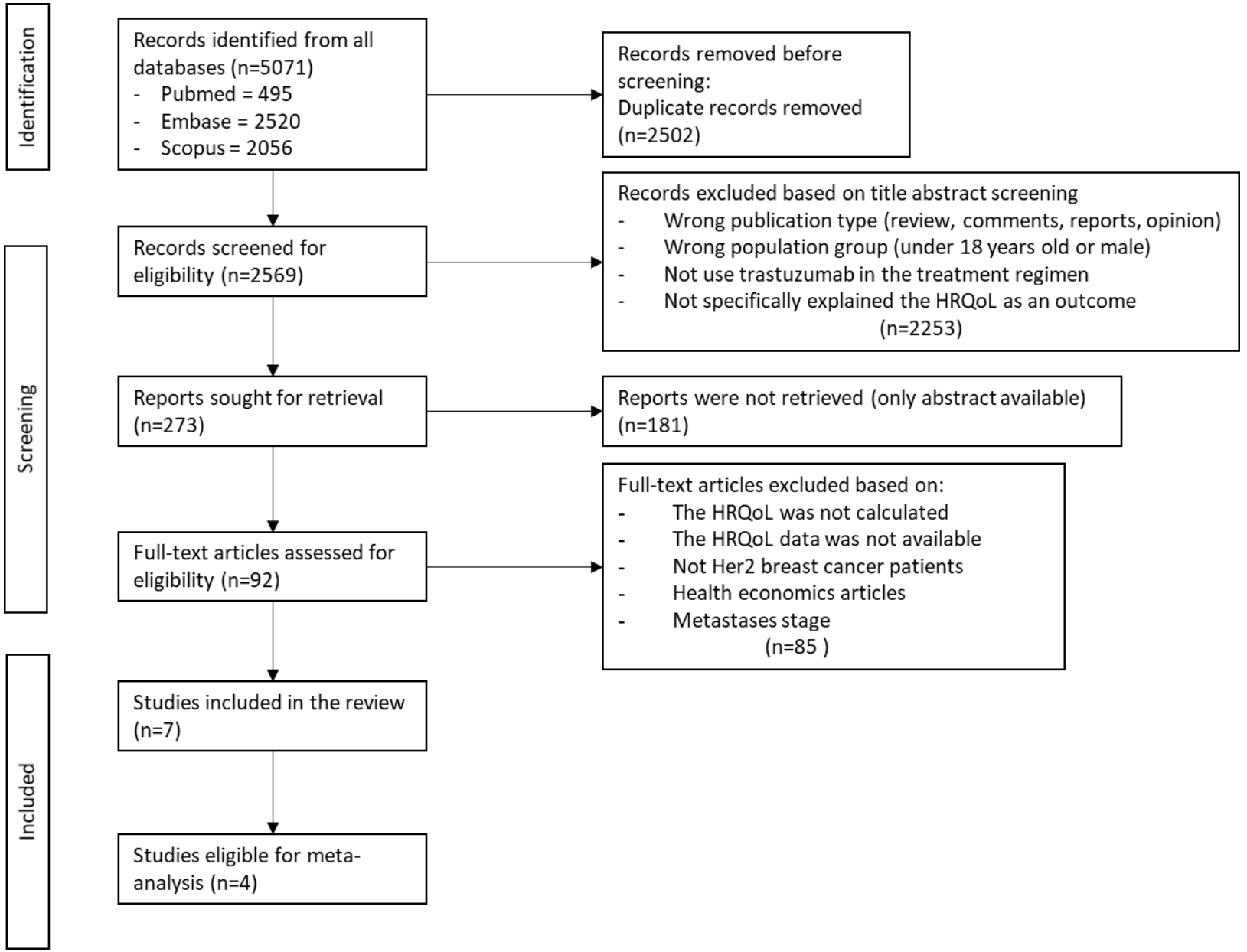
Review question

What is the Quality of Life and how does it translate into Quality Adjusted Life Years of breast cancer patients using Trastuzumab?

Searches

The following electronic databases will be used for a systematic search: PubMed, Embase, and Scopus. The literatures will be considered, including conference abstract, conference paper and ongoing clinical trials. The search strategies will only include terms related to the major domains of: a) breast cancer, b) Trastuzum

Prisma diagram



Study Characteristics

No	Author, year	Study design	Type of Instrument	Follow-up/ study period	Intervention/Treatment Regimen
1	Au et al[41], 2013	Randomised controlled trial	EORTC-QLQ-C30 BR-23	12 months	Doxorubicin 60mg/m2 and cyclophosphamide 600mg/m2 for four cycles followed by docetaxel 100mg/m2 for four cycles; nbaseline= 841, nfollowup=610
					Doxorubicin 60mg/m2 and cyclophosphamide 600mg/m2 for four cycles followed by docetaxel 100mg/m2 for four cycles and trastuzumab 4mg/kg loading dose and 2mg/kg weekly for 1 year; nbaseline=920, nfollowup=687
2	Conte et al[40], 2020	Randomised controlled trial	EORTC-QLQ-C30 BR-23	12 months	Trastuzumab 6mg/kg IV every 3 weeks and adjuvant endocrine; nbaseline=632, nfollowup=384
					T-DM1 3,6 mg/kg IV every 3 weeks and adjuvant endocrine; nbaseline=655, nfollowup=430
3	Trinca et al[43], 2019	Cross sectional	EORTC-QLQ-C30	April-November 2016	Treatment regimens with monoclonal antibodies: doxorubicin + cyclophosphamide + docetaxel + trastuzumab (N = 2); trastuzumab monotherapy (N = 7); docetaxel + trastuzumab + pertuzumab (N = 2); capecitabine + trastuzumab (N = 1); TDM-1 (N = 1); paclitaxel + trastuzumab (N = 1); docetaxel + trastuzumab (N = 4); Ntotal=18
4	Sawaki et al[39], 2020	Randomised controlled trial	FACT-G	3 years	Trastuzumab 8mg/kg and a maintenance dose of 6mg/kg every 3 weeks for 1 year; nbaseline=135, nfollowup=116
5	Syrios et al[44], 2018	Cross-sectional	EORTC-QLQ-C30 BR-23	2015-2016	Subcutaneous trastuzumab 600 mg every 3 weeks + chemotherapy + endocrine therapy; n=17
					Intravenous trastuzumab 6 mg/kg every 3 weeks after a loading dose of 8 mg/kg + pertuzumab ± chemotherapy + endocrine therapy; n=21
6	Taira et al[42], 2021	Randomized controlled trial	FACT-G	36 months	Trastuzumab monotherapy; N=137
7	Earl et al[38], 2000	Randomized controlled trial	EQ-5D-3L	24 months	6 months Trastuzumab (9 cycles); N=2043

Profile of Health-related Quality of Life for RCTs

No	Author, year	Mean change of baseline during chemotherapy	Mean change of baseline after chemotherapy	Comments
1	Au, et al[41]; 2013	Doxorubicin, Cyclophosphamide, Docetaxel, Trastuzumab -5.2 (2.868)	Doxorubicin, Cyclophosphamide, Docetaxel, Trastuzumab 2.8 (1.544)	General health: the deterioration from the baseline was not significant. After 12 months shown an improvement
		Doxorubicin, Cyclophosphamide, Docetaxel -7.1 (3.916)	Doxorubicin, Cyclophosphamide, Docetaxel 3.7 (2.041)	Physical functioning: TCH arm exhibited a significant improvement from baseline in the mid of point observations
				Systemic side effects: significant decrease from baseline for all intervention groups at mid point. After 12 months, an improvement was shown, HRQoL recovered in all domaina (GH, PF, SE)
2	Conte, et al[40]; 2020	Trastuzumab, adjuvant endocrine 0.6 (14.052)	Trastuzumab, adjuvant endocrine 3.2 (15.376)	GH and PFS: Maintenance for both arms until 12 months of follow-up
		T-DM1, adjuvant endocrine -1.9 (14.257)	T-DM1, adjuvant endocrine 2.8 (15.618)	the mean change from baseline not exceed the threshold in T-DM1 arm
				a significant deterioration more depicted in the T-DM1 arm in the fatigue, nausea, appetite loss, constipation, pain, systematic therapy side effects domains
				mean scores generally returned to the baseline levels after withdraw the treatment
3	Sawaki, et al[39]; 2020	Not reported	Clinically meaningful HRQoL improvement rate at 2 months (38% for trastuzumab monotherapy v 15% for trastuzumab plus chemotherapy; P 0.01), and at 1 year (43% v 25%; P 0.021). There was no significant difference between the two arms at 3 years	Significant improvement of HRQoL in Trastuzumab monotheraphy arm at 2 months and 1 year
4	Taira, et al[42]; 2021	Trastuzumab monotherapy 80.4 (15.0)	Trastuzumab monotherapy 79.1 (17.0)	Trastuzumab monotherapy lead to a significant improvement in general health
		Trastuzumab with chemotherapy 74.5 (15.9)	Trastuzumab with chemotherapy 78.5 (16.9)	Trastuzumab plus chemotherapy lead to a meaningfully deterioration of QoL in the first 36 months of follow-up
				After 36 months, a deterioration was not shown in both groups
5	Earl, et al[38]; 2020	Not reported	the general health is shown to decrease during the first three months in both arms	A comparative of general health profile in both intervention groups

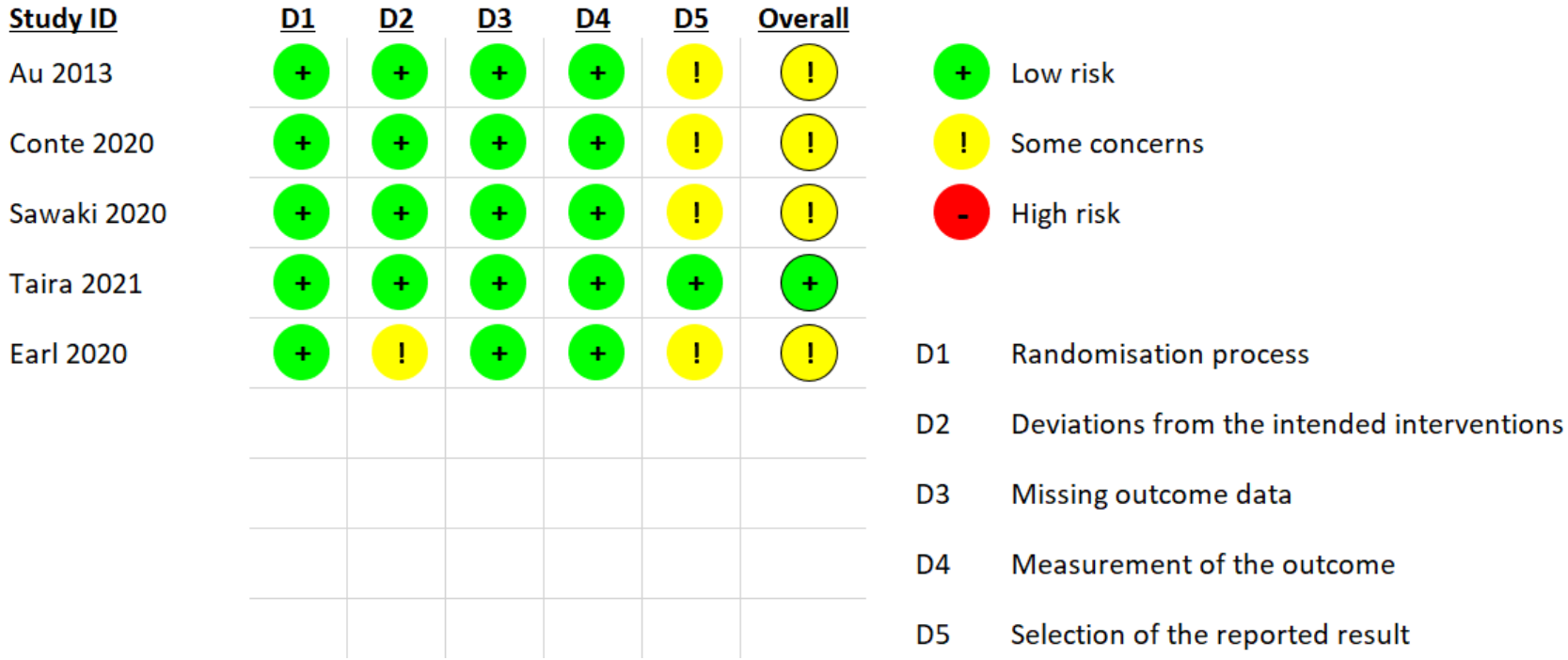
Studies included in meta-analysis

Profile of Health-related Quality of Life for Observational Studies

No	Author	Quality of Life instrument (s)	Total General Health	Comments
1	Syrios, et al[44]; 2018	EORTC-QLQ-C30 BR-23	Trastuzumab, chemotherapy, endocrine 73.8 (17.7)	Patients in trastuzumab arm experienced a better HRQoL
			Chemotherapy 65.4 (23.3)	Patients in trastuzumab arms experienced less diarrhea, nausea, vomiting, cognitive, and therapy side effects
2	Trinca, et al[43]; 2019	EORTC-QLQ-C30	Chemotherapy, monoclonal antibody 63.0 (22.2)	General health in trastuzumab arm was higher
			Chemoterapy 52.5 (17.6)	

All studies were included in meta-analysis

Methodological quality of RTCs (using RoB 2)



Methodological quality of Observational Studies (using STROBE checklist)

Sample size of the two studies was not calculated

A problem of reporting the missing data

The number of outcomes was only shown in the one-time point of the study

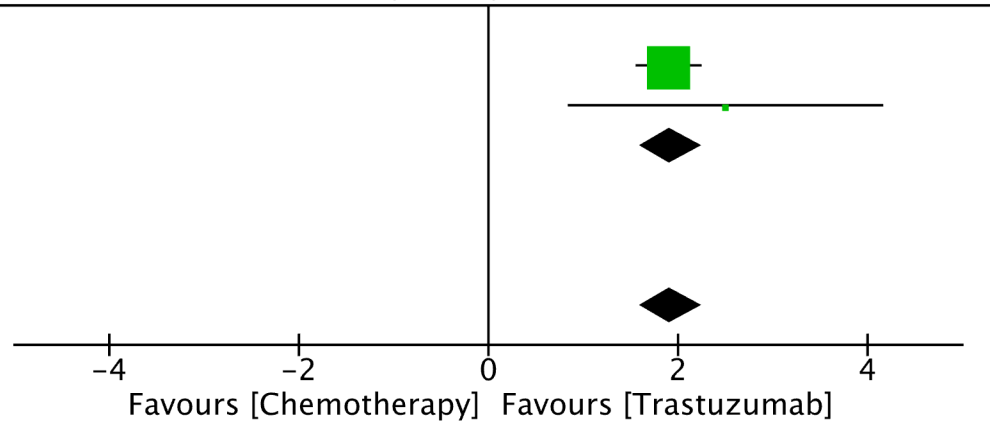
The transparency becomes important in observational studies

Main findings

- HRQoL profile was measured by EORTC-QLQ-C390 from baseline until during treatment
  - Patients in Trastuzumab group showed less adverse events
  - A deterioration of HRQoL profile was more depicted in control group
  - Systemic side effects domains demonstrated a significant increase for all control group

Results

Study or Subgroup	Trastuzumab Mean	SD	Total	Chemotherapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Global health status								
Au	-5.2	2.868	846	-7.1	3.916	783	96.0%	1.90 [1.56, 2.24]
Conte	0.6	14.052	558	-1.9	14.257	571	4.0%	2.50 [0.85, 4.15]
Subtotal (95% CI)			**1404**			**1354**	**100.0%**	**1.92 [1.59, 2.25]**
Heterogeneity: $Chi^2 = 0.49$, df = 1 (P = 0.49); $I^2 = 0\%$								
Test for overall effect: Z = 11.47 (P < 0.00001)								
Total (95% CI)			**1404**			**1354**	**100.0%**	**1.92 [1.59, 2.25]**
Heterogeneity: $Chi^2 = 0.49$, df = 1 (P = 0.49); $I^2 = 0\%$								
Test for overall effect: Z = 11.47 (P < 0.00001)								
Test for subgroup differences: Not applicable								



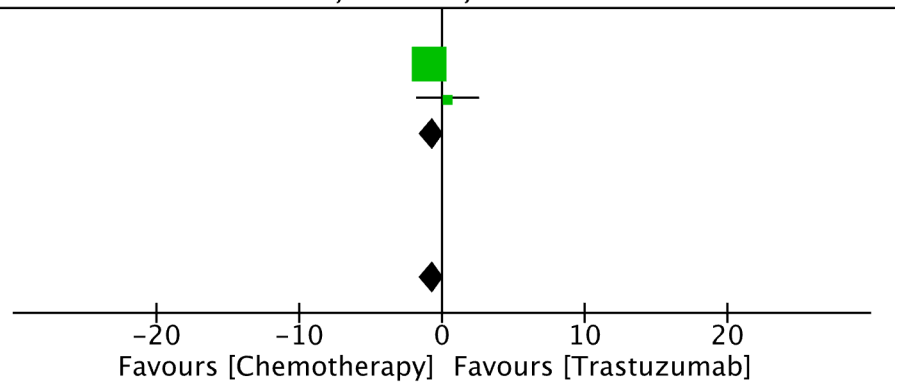
Pooled analysis of the mean change of baseline during treatment between Trastuzumab-containing regimen and chemotherapy

- The lower score of the mean change of baseline of HRQoL in the control arm was associated with the adverse events caused by chemotherapy.
- The patients using anthracycline-cyclophosphamide based chemotherapy and docetaxel experienced a lower score of general health, physical functioning, and more systemic side effects during treatment due to the cardiotoxicity, fatigue, and nausea.

After one year of treatment

- The total general health was generally maintained in both arms

Study or Subgroup	Trastuzumab Mean	SD	Total	Chemotherapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 Global health status								
Au	2.8	1.544	687	3.7	2.041	610	84.7%	-0.90 [-1.10, -0.70]
Conte	3.2	15.376	384	2.8	15.618	430	15.3%	0.40 [-1.73, 2.53]
Subtotal (95% CI)			**1071**			**1040**	**100.0%**	**-0.70 [-1.62, 0.22]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 1.42$, df = 1 (P = 0.23); $I^2 = 29\%$								
Test for overall effect: Z = 1.50 (P = 0.13)								
Total (95% CI)			**1071**			**1040**	**100.0%**	**-0.70 [-1.62, 0.22]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 1.42$, df = 1 (P = 0.23); $I^2 = 29\%$								
Test for overall effect: Z = 1.50 (P = 0.13)								
Test for subgroup differences: Not applicable								

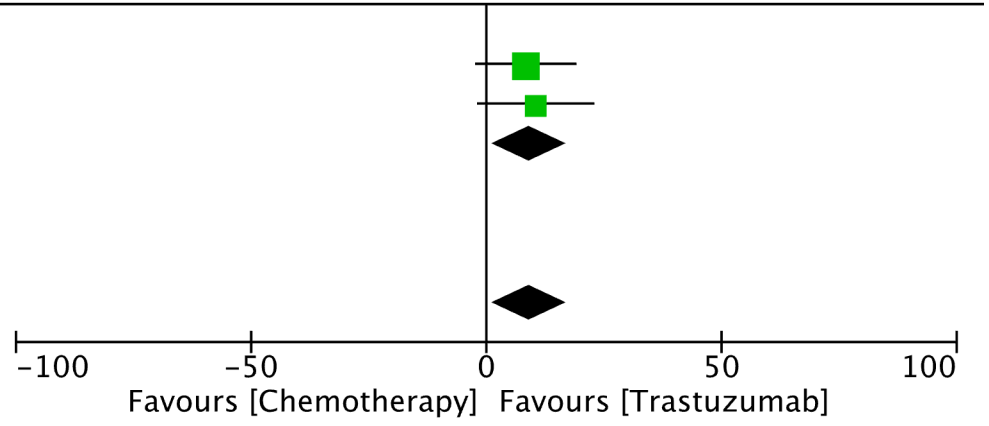


Pooled analysis of the mean change of baseline after treatment (12-months of follow-up) between Trastuzumab-containing regimen and chemotherapy

The total general health (observational studies)

- Measured by FACT-G questionnaire **during treatment**
- HRQoL profile was higher in trastuzumab groups

Study or Subgroup	Trastuzumab Mean	SD	Total	Chemotherapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Global health status								
Syrios	73.8	17.7	36	65.4	23.3	27	57.4%	8.40 [-2.12, 18.92]
Trinca	63	22.2	18	52.5	17.6	27	42.6%	10.50 [-1.72, 22.72]
Subtotal (95% CI)			**54**			**54**	**100.0%**	**9.29 [1.32, 17.27]**
Heterogeneity: $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0\%$								
Test for overall effect: Z = 2.29 (P = 0.02)								
Total (95% CI)			**54**			**54**	**100.0%**	**9.29 [1.32, 17.27]**
Heterogeneity: $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0\%$								
Test for overall effect: Z = 2.29 (P = 0.02)								
Test for subgroup differences: Not applicable								



Pooled analysis of total general health during treatment between Trastuzumab-containing regimen and chemotherapy

Other findings

- Elderly patients receiving **trastuzumab monotherapy** experienced a clinically meaningful total general health (using FACT-G).
- Fewer adverse events appeared during the first 36 months of observation and an impressive profile in all functional domains.
- After 36 months, the diminishing adverse effects were observed and did not affect the general health
- A significant deterioration was shown in trastuzumab plus chemotherapy group at two months and one year of treatment.

- When evaluating treatment benefits, it is essential to consider the effect on HRQoL of adding a new drug to the treatment regimen
- Present review highlights that the addition of trastuzumab to chemotherapy did not lead to a detrimental effect on the patient's HRQoL.
- During treatment, the impairment of HRQoL the patients receiving trastuzumab was less shown meaningfully compared to the regiment without trastuzumab.
- The profile of HRQoL remained stable and seems to have a long-term of beneficial effect in terms of the patients perception after one-year of follow-up time
- The benefits of trastuzumab in the improvement of overall survival should balance on the impact of patients HRQoL.

Strength

- It is the first systematic review and meta-analysis performing the HRQoL of the Trastuzumab in the early stage of breast cancer management
- Three large electronic databases to conduct a systematic search and language limitation as well as the year of publication were the strict inclusion criteria applied in this review
- The quality of the studies was rate as good despite of the some missing methodology in the observational studies

Limitations

- In regards with the meta-analysis presented in this study, despite the high of homogeneity in the calculation, there were only two studies included in the pooled analysis in which have less power to interpret the overall result.
- The variety of the treatment regimen both in the trastuzumab and control group may affect the different profile of HRQoL.

Conclusion

Trastuzumab as a targeted therapy resulted a potential improvement of HRQoL in the Her2 early stage of breast cancer patients.

The benefits of trastuzumab in the regimen of treatment in the long term of HRQoL supports the efficacy and the effectiveness in the early breast cancer management as well as the less adverse events occurred during receiving the treatment.

THANK YOU

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