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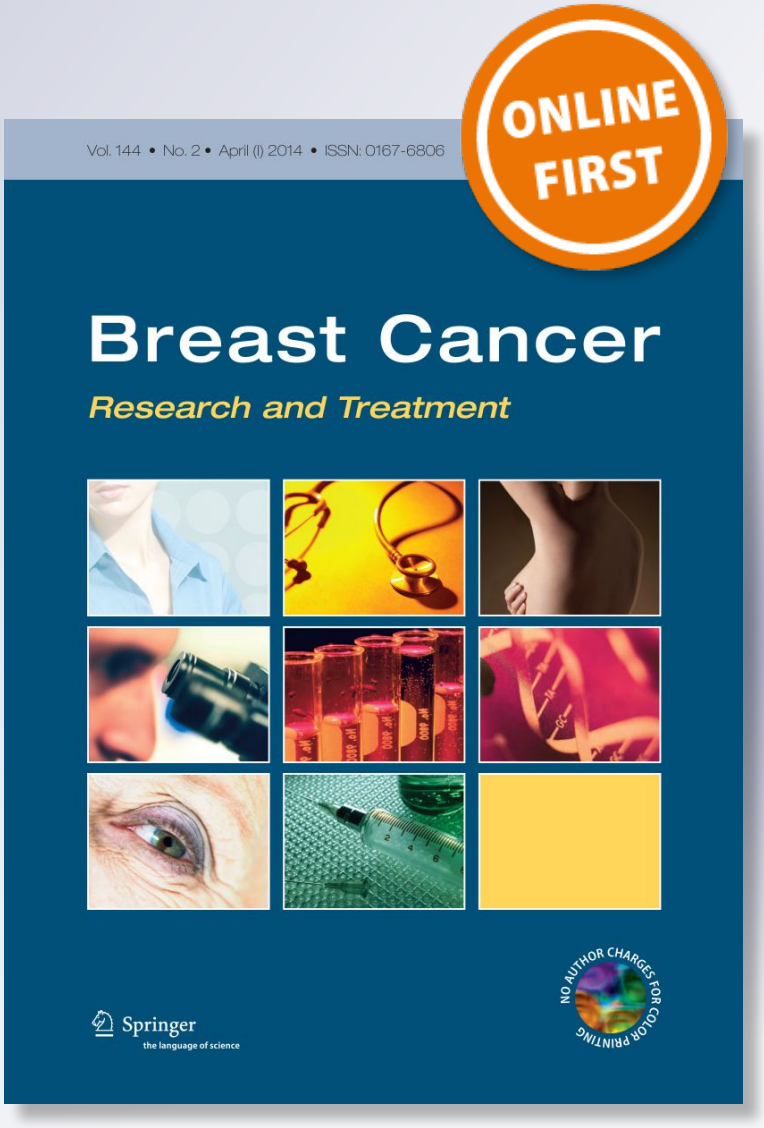

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REVIEW

Influence of comorbidity on chemotherapy use for early breast cancer: systematic review and meta-analysis

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Abstract
Purpose Patients with early breast cancer and coexistent comorbidities generally experience worse prognosis which may be in part related to inferior treatment. Randomised data on chemotherapy use and tolerance in comorbid patients are limited. We aimed to review the available literature regarding the use of chemotherapy in such patients.
Methods A systematic search of databases was performed for English-language articles evaluating the impact of comorbidity on chemotherapy use for early breast cancer. Comorbidity was assessed as a specific condition, summary count or index. Outcomes of interest were receipt of chemotherapy, change in chemotherapy delivery and occurrence of toxicity.
Results Sixty studies met inclusion criteria for systematic review. Thirty-three studies evaluated receipt of chemotherapy, with 19 reporting reduced treatment, particularly with higher levels of comorbidity. Meta-analysis of 10 eligible studies returned odds ratios (OR's) of 0.88 [95% confidence interval (CI) 0.80–0.96] and 0.63 (95% CI 0.49–0.80) for receipt of chemotherapy by patients with comorbidity scores of 1 and ≥2, respectively, compared with no comorbidity. Comorbidity had a generally adverse impact on the quality of chemotherapy delivery, although outcomes were heterogeneous. Toxicity was greater in patients with comorbidity, with 10 out of 13 studies reporting greater odds of toxicity or hospitalisation during chemotherapy. Meta-analysis of three studies addressing chemotherapy-associated hospitalisation produced OR's of 1.42 (95% CI 1.20–1.67) and 2.23 (95% CI 1.46–3.39) for comorbidity scores of 1 and ≥2, respectively.
Conclusions Compared with their non-comorbid counterparts, comorbid patients with early breast cancer receive less quality adjuvant chemotherapy and experience greater toxicity.

Keywords Comorbidity · Breast cancer · Chemotherapy · Systematic review · Meta-analysis

Introduction

Breast cancer is the most frequently diagnosed cancer and cause of cancer death among women worldwide [1]. Like many cancers, the risk of developing and dying from breast cancer increases with age [2]. In parallel with increased vulnerability to breast cancer, increasing age also confers greater risk for the development of a number of other chronic health conditions [3]. Given projections of an ageing population [4], the absolute number of elderly breast cancer patients with coexistent comorbidities is expected to increase over the coming decades [5].

Depending on disease subtype, curative treatment for breast cancer requires multicomponent care to minimise recurrence and extend survival. For many patients with higher risk disease, this includes chemotherapy, the benefits of which have been shown by multiple randomised

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controlled trials [6]. The absolute benefits of chemotherapy in older women remain unknown however, with few women older than 70 years included in these trials [6]. Treatment guidelines such as the St. Gallen Consensus do not set an upper age limit on the use of chemotherapy, but acknowledge that treatment decisions should be individualised, taking account of comorbidity and life expectancy [7]. However, comorbid patients with cancer are also largely excluded from clinical trials of chemotherapy [8], leaving unanswered questions about the effectiveness and tolerance of chemotherapy in such patients.

In this article, we sought to review existing knowledge regarding the utilisation of chemotherapy for early breast cancer by patients with concurrent comorbidity. Our specific objectives were to (1) obtain an estimate of the odds of chemotherapy receipt, (2) examine changes in the quality of chemotherapy delivered and (3) determine the occurrence of chemotherapy-associated toxicity, all stratified by level of comorbidity severity.

Methods

Systematic review and meta-analysis were performed in accordance with PRISMA guidelines [9].

Study selection

Types of studies

English-language articles evaluating the impact of comorbidity on chemotherapy use and outcomes in early breast cancer were identified. A systematic search of MEDLINE (Ovid), Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials from inception to 15 March 2016 was performed using comprehensive search strategies incorporating MeSH headings and key words relating to breast cancer, comorbidity and chemotherapy. The reference lists of included studies and relevant articles were hand-searched to identify additional eligible publications. Both randomised and non-randomised studies were included. Qualitative studies, abstracts, reviews, editorials and case studies were excluded.

Types of participants

The search targeted articles which compared early-stage breast cancer patients with and without concurrent comorbidity. Where a study included patients with in situ and/or metastatic disease, only outcomes relating to those with stages I–III malignancy were considered. Studies which did not differentiate between early and distant disease were excluded. Comorbidity was assessed as a specific condition, summary count or index score. Studies using measures of functional status without measurement of comorbidity were excluded.

Types of interventions

Articles pertaining to the use of neoadjuvant and/or adjuvant chemotherapy were included. Studies addressing multimodality treatment were retained, but only information related to chemotherapy was abstracted.

Types of outcome measures

An estimate of effect and precision for the following outcome measures was required for inclusion:

- *Receipt* defined as receipt of chemotherapy, guideline concordance with respect to receipt of chemotherapy or recommendation for chemotherapy.
- *Change in delivery* defined as delay to the receipt of chemotherapy, delays during the course of treatment, measures of dose intensity, dose reductions or regime. For articles addressing regime, comparisons were abstracted for the most commonly used schedules in early breast cancer: anthracycline-based, taxane-based, combination anthracycline/taxane, and cyclophosphamide, methotrexate and fluorouracil (CMF) regimes.
- *Toxicity* defined as serious toxic events, febrile neutropenia, hospital admissions occurring during the course of chemotherapy treatment or non-completion of chemotherapy.

Data abstraction

Titles and abstracts were manually screened by one reviewer (ME) using explicit pre-determined criteria. Where eligibility remained unclear, the content of the full article was assessed independently by two further reviewers (IC and RL) and a final decision reached by consensus. Data were extracted from each eligible study by one reviewer (ME) using a standardised electronic data collection form.

Quality assessment

Quality was judged based upon how the study examined the outcomes of interest to this review. The quality of randomised controlled trials was assessed using the risk of bias assessment tool from the Cochrane handbook for

systematic reviews of interventions [10]. For non-randomised cohort studies, an adapted Newcastle–Ottawa quality assessment scale was used [11]. Assessment was based upon selection (representativeness/selection of the cohorts and demonstration of a prospective design), comparability (statistical adjustment for age and stage confounders) and outcome (outcome ascertainment and sufficiency of follow-up) domains. No study was excluded based on quality assessment.

Data synthesis and analysis

Systematic review

Narrative synthesis was used to summarise the main outcomes of interest, stratified by level of comorbidity severity. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were preferentially derived from raw data or extracted. Where possible, the odds of each outcome measure for patients with varying levels of comorbidity severity were compared to a reference group of patients without comorbidity. The most adjusted estimate of effect was presented. p values <0.05 were considered statistically significant.

Meta-analysis

Meta-analysis was performed where three or more appropriate studies assessing a specific outcome measure existed. To facilitate comparison of studies with different measures of comorbidity severity, two subgroups for each meta-analysis were defined: patients with a comorbidity count or index score = 1 and patients with a score ≥2. Studies were required to statistically adjust for both age and stage (or alternatively, tumour size plus lymph node status) confounders. Where a study reported on subgroups with different histopathological features, the subgroup with the most advanced disease was selected for meta-analysis. These subgroups were selected for particular focus because the proportional impact of chemotherapy on cancer outcomes is greater in higher risk disease than in earlier stage, where the likelihood of cure is superior and the omission of chemotherapy can sometimes be considered. Likewise, where a study performed subgroup analysis based on age, the youngest age category was selected for meta-analysis. Mortality in younger women with breast cancer is more likely to be attributable to breast cancer itself than in older women, where death is more likely to be due to a competing cause [12, 13]. As such, treatment decisions in younger patients have relatively greater impact on breast cancer-specific mortality. With these criteria, two meta-analyses were possible: receipt of chemotherapy and hospital admission due to chemotherapy-associated toxicity. The software package RevMan 5.3 [14] was used to pool the results from eligible studies for meta-analysis. Due to the non-randomised design of the included studies, a generic inverse variance method was used to calculate effect size, producing a log [OR]. Random effects analysis was utilised. The presence of statistical heterogeneity of the included studies was assessed using χ^2 tests at a significance level of $p < 0.05$ and quantified using I^2 statistics. Funnel plots were produced to assess likelihood of reporting bias.

Results

Description of studies

The electronic database searches yielded 2251 records after removal of duplicates. A further 11 studies were identified from other sources. One hundred and seventy-three full text articles were assessed, with a 60 studies meeting eligibility criteria for inclusion in the systematic review (PRISMA flowchart of study selection shown in Fig. S1: supplemental material). Characteristics of the included studies are summarised in Table 1. Studies were relatively recent, with all but one published later than 2000. A majority were conducted in North America (82%). Two were multi-centre randomised controlled trials, while the remainder were observational cohorts, half of which used cancer registry data linked with an administrative database. Of these population-based cohorts, 17 (55%) utilised the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The median sample size was 1432 (range 62–107,587).

More than 98% of study participants were female. Approximately, half of the studies imposed a minimum age limit on participants ranging from 50 to 70 years. Of the 42 studies which recorded ethnicity, 37 (88%) comprised a majority Caucasian population. Seven studies recorded Eastern Cooperative Oncology Group performance status, with each reporting scores of 0–1 in greater than 95% of patients. Twenty-one studies specified a requirement for an incident breast cancer.

One-third of studies assessed multimodality treatment, including seven evaluating trastuzumab in combination with adjuvant chemotherapy. Neoadjuvant chemotherapy with or without adjuvant chemotherapy was addressed in seven studies. Depending on patient population and definition, the prevalence of comorbidity ranged widely, from 0.66 to 62.5%. The Charlson comorbidity index or its modification was used most commonly (67% of studies), while a summary count of comorbidities was used in 17%. Eleven studies examined the impact of specific comorbidities, the most common of which were diabetes,

Table 1 Description of included studies

Studies	Design	Nos.	Population	Treatment	Comorbidity (%)[a]	Outcomes
Banerjee 2007 [15]	Retrospective single-centre cohort	651	Local–regional stage	Surg ± XRT, adjuvant chemo, HT	CC (62.5)	R
Barcenas 2012 [16]	Retrospective population-based cohort	7399	Age ≥66, stages I–III	Chemo[b]	Klabunde-CCI (23.7)	Q
Barcenas 2014 [17]	Retrospective population-based cohort	3567	Age ≥66, stages I–III	Chemo[b]	Klabunde-CCI (27.7)	Q, T
Bhargava 2009 [18]	Retrospective population-based cohort	15,454	Age ≥65, stages II–IIIa, LN+	Adjuvant chemo	CC (35.6)	R
Bowles 2012 [19]	Retrospective population-based cohort	12,500	Mean age 60, local–regional stage	Adjuvant chemo ± trastuzumab	Deyo-CCI (29.0)	R, Q
Braithwaite 2012 [20]	Retrospective population-based cohort	2272	Age ≤79, stage I (>1 cm) –IIIa	Surg, XRT, chemo[b], HT	Katz-CCI (52.6), HTN	R
Brewster 2011 [21]	Retrospective multi-centre cohort	9527	Age ≤70, stages I–III	Adjuvant chemo	Katz-CCI (15.1)	R
Carroll 2014 [22]	Retrospective multi-centre cohort	374	Stage <IV	Adjuvant chemo, trastuzumab	CC	Q, T
Chan 2012 [23]	Retrospective single-centre cohort	189	Median age 54, stages I–IIIa	Adjuvant chemo	CC (38.9)	T
DeMichele 2003 [24]	Retrospective single-centre cohort	208	Age ≥50, early stage	Adjuvant chemo	CCI (32.7), previous malignancy	R
Doyle 2005 [25]	Retrospective population-based cohort	31,748	Age ≥65, stages I–III	Adjuvant chemo	Klabunde-CCI (32.0)	R, Q
Du 2015 [26]	Retrospective population-based cohort	14,440	Age 65–90, stages I–IIIa, ER/PR−	Adjuvant chemo	Klabunde-CCI (36.2)	R, Q
Elkin 2006 [27]	Retrospective population-based cohort	5081	Age ≥66, stages I–III, ER/PR−	Adjuvant chemo	Romano and Klabunde-CCI (31.1)	R
Enewold 2012 [28]	Retrospective population-based cohort	2699	Local–regional stage	Surg ± XRT, chemo[b], HT	CCI (25.5)	R
Enger 2006 [29]	Retrospective population-based cohort	1859	Age ≥65, stages I–IIb	Surg, XRT, adjuvant chemo, HT	CCI (32.0)	R
Enright 2015 [30]	Retrospective population-based cohort	8359	Mean age 53.7, stages I–III	Adjuvant chemo, trastuzumab	Deyo-CCI (8.10)	Q, T
Fedewa 2010 [31]	Retrospective population-based cohort	107,587	Stages I–III	Adjuvant chemo	Deyo-CCI (10.5)	Q
Freedman 2014 [32]	Retrospective population-based cohort	2106	Age ≥66, stages I–III, Her2+	Adjuvant chemo + trastuzumab	Klabunde-CCI (34.2)	Q
Garg 2009 [33]	Retrospective single-centre cohort	62	Age ≥70, stages I–II	Adjuvant chemo	CCI (19.4)	Q

Table 1 continued

Studies	Design	Nos.	Population	Treatment	Comorbidity (%)[a]	Outcomes
Gennari 2004 [34]	Prospective single-centre cohort	2999	Early stage	Adjuvant chemo, HT	CC	R
Giordano 2005 [35]	Retrospective single-centre cohort	1568	Age ≥55, stages I–IIIa	Surg, XRT, adjuvant chemo, HT	CCI (30.4)	R
Giordano 2006 [36]	Retrospective population-based cohort	41,390	Age ≥65, stages I–III	Adjuvant chemo	Klabunde-CCI (31.5)	R
Gorin 2005 [37]	Retrospective population-based cohort	50,460	Age ≥65, stages I–III	Surg, XRT, chemo[b]	Alzheimer's disease (3.83)	R
Griffiths 2014 [38]	Retrospective population-based cohort	48,015	Age ≥65, stages I–III	Adjuvant chemo	Klabunde-CCI (32.8), undetected index (10.1)	R
Griggs 2003 [39]	Retrospective multi-centre cohort	489	Stages I–III	Adjuvant chemo	CCI (13.7)	Q
Griggs 2005 [40]	Retrospective multi-centre cohort	9672	Mean age 51, stages I–III	Adjuvant chemo	CC (0.66)	Q, T
Griggs (a) 2007 [41]	Prospective multi-centre cohort	957	Mean age 53.2, stages I–III	Adjuvant chemo	CCI (15.7)	Q
Griggs (b) 2007 [42]	Prospective multi-centre cohort	764	Mean age 53.2, stages I–III	Adjuvant chemo	CCI (15.6)	Q
Griggs 2014 [43]	Retrospective population-based cohort	397	Stages I–III	Adjuvant chemo	Katz-CCI (26.2)	Q
Hawfield 2006 [44]	Retrospective single-centre cohort	273	Age >55, stages I–IIb	Adjuvant chemo	CCI (24.9)	R
Hershman 2005 [45]	Retrospective population-based cohort	472	Stages I–II	Adjuvant chemo	Deyo-CCI (19.3)	Q
Hershman 2006 [46]	Retrospective population-based cohort	5003	Age ≥65, stages I–II	Adjuvant chemo	Klabunde-CCI (26.7)	Q
Javid 2014 [47]	Retrospective population-based cohort	24,023	Age ≥65, stages I–II	Adjuvant chemo	CCI (27.9)	R
Jitawatanarat 2014 [48]	Retrospective single-centre cohort	177	Early stage, Her2+	Neo/adjuvant chemo + trastuzumab	CCI, CVD (4.0), HTN (28.8), DM (10.2)	Q
Kadakia 2015 [49]	Retrospective population-based cohort	11,322	Age ≥66, stages I–III	Adjuvant chemo	Klabunde-CCI (24.4), renal failure (1.35)	Q
Kaplan 2012 [50]	Retrospective single-centre cohort	483	Mean age 48.2, stages I–IIIa	Adjuvant chemo	Type 2 DM (11.1)	Q
Kimmick 2006 [51]	Retrospective population-based cohort	974	Stages I–III	Surg, XRT, adjuvant chemo	D'Hoore-CCI	R
Klepin 2014 [52]	Prospective cohort within an RCT	329	Age ≥65, stages I (>1 cm)–III	Adjuvant chemo	OARS comorbidity burden score	Q, T
Kurian 2013 [53]	Retrospective population-based cohort	6004	Stages I–III	Chemo[b], trastuzumab	CCI-Quan (22.8), DM (11.3), neuropathy (3.1), CVD (7.2)	R, Q

Table 1 continued

Studies	Design	Nos.	Population	Treatment	Comorbidity (%)[a]	Outcomes
Land 2012 [54]	Retrospective population-based cohort	39,943	Early stage	Adjuvant chemo, HT	CCI (20.4)	R
Lipscomb 2012 [55]	Retrospective population-based cohort	868	Stages I–IIIa	Adjuvant chemo	CC (48.0)	R, T
Ma 2009 [56]	Retrospective single-centre cohort	866	Age ≥60, early stage	Surg, XRT, adjuvant chemo, HT	CC (51.0)	R
Mandelblatt 2000 [57]	Prospective multi-centre cohort	718	Age ≥67, stages I–IIb	Surg ± XRT, chemo[b], HT	ICED	R
Mandelblatt 2010 [58]	Prospective multi-centre cohort	934	Age ≥65, early stage (>1 cm)	Neo/adjuvant chemo	OARS CC (>2: 57)	R
Muss 1992 [59]	Prospective population-based cohort	305	Age ≤79, stage II, LN+	Surg ± XRT, chemo[b], HT	Presence/absence (44.0)	R
Nagel 2003 [60]	Prospective population-based cohort	1228	Age ≥50, stages I–IIb	Adjuvant chemo, HT	D'Hoore-CCI (15.8)	R
Nuzzo 2008 [61]	Safety analysis of a phase III RCT	101	Age 65–79, early stage	Adjuvant chemo	CCI (≥2: 74.8)	T
O'Connor 2012 [62]	Retrospective single-centre cohort	204	Age ≥65, stages I–III	Neo/adjuvant chemo	CCI, HTN	Q, T
Rocque 2012 [63]	Retrospective multi-centre cohort	200	Mean age 51.4, stages I–III, Her2+	Neo/adjuvant chemo + trastuzumab	DM (8.0), CVD (5.0), HTN (28.0)	Q
Sabatino 2014 [64]	Retrospective population-based cohort	5834	Stages I–III	Surg ± XRT, adjuvant chemo, HT	Type 2 DM (10.2)	R
Schwenkglenks 2011 [65]	Prospective multi-centre cohort	444	Mean age 53.5, stages I–III	Neo/adjuvant chemo	Vascular (19.6)	T
Shayne 2006 [66]	Retrospective multi-centre cohort	3707	Median age 52, early stage	Adjuvant chemo	CC (3.7), renal disease	Q
Shayne 2009 [67]	Prospective multi-centre cohort	1224	Stages I–III	Chemo[b]	Unweighted CCI (14.5)	Q, T
Simon 2012 [68]	Retrospective population-based cohort	2234	Mean age 61.2, stages I–III	Adjuvant chemo	Deyo-CCI (30.8)	R, Q
Srokowski 2009 [69]	Retrospective population-based cohort	70,781	Age ≥66, stages I–III	Adjuvant chemo	Klabunde-CCI (19.9), DM (20.4)	R, Q, T
Von Minckwitz 2015 [70]	Safety analysis of a phase II RCT	391	Age ≥65, stages I–III	Adjuvant chemo	CCI (28.6)	Q, T
Wheeler 2012 [71]	Retrospective population-based cohort	6678	Age ≥65, stages II–III, ER/PR−	Adjuvant chemo	Klabunde-CCI	R
Woodard 2003 [72]	Retrospective single-centre cohort	480	Stages I–III	Adjuvant chemo	CCI (16.3)	R
Zauderer 2009 [73]	Retrospective single-centre cohort	162	Age ≥60, stages I–III	Neo/adjuvant chemo	CCI (27.2)	T
Zhu 2015 [74]		1296	Mean age 50, stages I–III	Adjuvant chemo	CC (29.5)	R

Table 1 continued

Studies	Design	Nos.	Population	Treatment	Comorbidity (%)[a]	Outcomes
	Retrospective single-centre cohort					

CC comorbidity count, *CCI* Charlson comorbidity index, *chemo* chemotherapy, *CVD* cardiovascular disease, *DM* diabetes mellitus, *ER* estrogen receptor, *ESRD* end-stage renal disease, *Her2+* Her2 receptor positive, *HT* hormone therapy, *HTN* hypertension, *ICED* index of coexistent diseases, *LN* lymph node, *PR* progesterone receptor, *Q* quality, *OARS* older Americans resources and services multidimensional functional assessment, *R* receipt, *RCT* randomised controlled trial, *surg* surgery, *T* toxicity, *XRT* radiotherapy

[a] Percentage with comorbidity (if reported); defined as the presence of any condition, comorbidity count ≥1 or index score ≥1

[b] Chemotherapy not otherwise specified as neoadjuvant or adjuvant

cardiovascular disease and hypertension. Approximately half of the studies made an assessment of comorbidity severity. Seventeen studies treated comorbidity as the primary exposure variable while the remainder considered it as a confounder in multiple regression modelling.

Study quality

Overall the quality of reporting among the non-randomised studies was good, with a median score of seven out of a total of nine (range 4–9) on the adapted Newcastle–Ottawa scale (Table S1: supplemental material). Representativeness and selection of the cohorts, ascertainment of comorbidity, assessment of outcomes and length of follow-up were generally well reported. However, most studies were retrospective (82%), and 45% made no statement about the completeness of subject follow-up. The majority of studies controlled for age and/or stage (74%). Due to their open label design, both randomised studies were at high risk of selection and performance bias, although attrition bias was low.

Receipt of chemotherapy

Of the 33 publications appraising this outcome (Table 2), 30 studies evaluated receipt of chemotherapy, 2 studies addressed guideline concordance [35, 64] with respect to receipt of chemotherapy and 1 considered recommendation for chemotherapy [24]. Overall, 19 (58%) studies reported a decrease in treatment for patients with some level of comorbidity compared to those without. The remaining studies showed no difference, with the exception of DeMichele 2003, who found that chemotherapy was recommended more frequently in patients with a previous malignancy (OR = 4.39), irrespective of the presence of other comorbidity [24].

Meta-analysis

Ten studies met inclusion criteria for meta-analysis of chemotherapy receipt (Fig. 1). A funnel plot for risk of publication bias was roughly symmetrical. The OR of receiving chemotherapy with a comorbidity index score/count = 1 (compared with a score = 0) (subgroup one) was 0.88 (95% CI 0.80–0.96) and 0.63 (95% CI 0.49–0.80) for participants with a score ≥2 (subgroup two). Heterogeneity was high across the two subgroups ($I^2 = 87\%$).

Change in chemotherapy delivery

Outcomes evaluated by the 24 studies considering a change in the quality of chemotherapy received (Table 3) were highly clinically heterogeneous, and as such formal meta-analysis was not possible. Outcomes were synthesised into three subgroups: delay, dose and regime.

Delay

Three studies evaluated delay to receipt of chemotherapy (defined as either >60 or >90 days from diagnosis), with one reporting an increased risk of delay with comorbidity [31] and the others finding no difference [46, 68]. Two studies [62, 66] addressed dose delays of greater than 7 days during the course of treatment, with one reporting more delays with comorbidity [62].

Dose

Four studies reported on first cycle dose reductions [39, 40, 42, 43] (defined as <85 or <90% of the expected dose for a given patients' body surface area), with two finding more reductions for patients with comorbidity [40, 43]. Three studies [52, 62, 66] evaluated dose reductions during the course of treatment, with one reporting more treatment modifications for patients with two or more comorbid conditions compared with none (59 vs. 46%, $p = 0.03$) [52], and another showing an increase in planned dose reductions of >10% for patients with renal disease (OR = 21.2) [66]. All seven studies addressing dose proportion [39, 40] (ratio of actual: expected doses) or relative dose intensity (RDI) [22, 39, 62, 66, 67] demonstrated no difference for patients with comorbidity.

Table 2 Receipt of chemotherapy by patients with comorbidity (selected results)

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Banerjee 2007	Receipt	Local stage: CC ≥2	1.03	0.37–2.85	Age, race, SES, tumour factors	No difference
		Regional stage: CC ≥2	2.28	0.64–8.12		
Bhargava 2009	Receipt (within 6 months)	Age 65–69: CC 1	**0.77**	**0.63–0.94**	Race, SES, year, region, treatment, tumour factors	Reduced treatment
		Age 65–69: CC ≥2	**0.31**	**0.24–0.41**		
		Age ≥80: CC 1	0.87	0.67–1.13		
		Age ≥80: CC ≥2	**0.63**	**0.45–0.88**		
Bowles 2012	Receipt	CCI 1	**0.83***	**0.75–0.92***	None	Reduced treatment
		CCI ≥3	**0.76***	**0.64–0.89***		
Braithwaite 2012	Receipt	CCI 1	**0.69***	**0.56–0.86***	None	Reduced treatment with comorbidity and HTN
		CCI ≥2	**0.50***	**0.40–0.62***	None	
		HTN	N/R	N/R		
Brewster 2011	Receipt chemo 'standard'	CCI ≥1	**0.68**	**0.56–0.83**	Age, ethnicity, BMI, centre, tumour factors	Reduced treatment
	Receipt chemo 'discretionary'	CCI ≥1	**0.60**	**0.44–0.81**	None	
DeMichele 2003	Chemo recommendation	CCI ≥1	0.45	0.17–1.22	Age, ER status	No difference
		Previous malignancy	**4.39**	**1.05–18.29**		Greater recommendation
Doyle 2005	Receipt	CCI 1	0.92	0.85–1.01	Age, year, heart disease, treatment, tumour factors	Reduced treatment with higher comorbidity
		CCI ≥2	**0.82**	**0.73–0.92**		
Du 2015	Receipt (within 12 months)	CCI 1	**0.83***	**0.77–0.90***	None	Reduced treatment
		CCI ≥3	**0.48***	**0.41–0.56***		
Elkin 2006	Receipt (within 6 months)	CCI 1	0.90	0.74–1.09	Age, race, SES, year, region, tumour factors	Reduced treatment with higher comorbidity
		CCI ≥2	**0.53**	**0.42–0.68**		
Enewold 2012	Receipt (within 6 months)	Local stage: CCI ≥2	0.80	0.6–1.2	Age, race, SES, treatment, ER/PR status	No difference
		Regional stage: CCI ≥2	0.80	0.4–1.6		
Enger 2006	Receipt	CCI 1–2	**0.56***	**0.39–0.82***	None	Reduced treatment
		CCI ≥3	**0.09***	**0.01–0.61***		
Gennari 2004	Receipt	CC 0 (vs. CC ≥2)	1.75	0.76–4.06	Age, comorbidity, treatment, tumour factors	No difference
		CVD	1.34	0.52–3.44		
		Non-CVD comorbidity	1.26	0.46–3.44		

Table 2 continued

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Giordano 2005	Guideline concordance	CCI ≥2	0.89	0.35–2.33	Age, race, SES, tumour factors	No difference
Giordano 2006	Receipt (within 12 months)	CCI 1	**0.76**	**0.68–0.84**	Age, ethnicity, year, region, tumour factors	Reduced treatment
		CCI ≥2	**0.49**	**0.41–0.57**		
Gorin 2005	Receipt	Alzheimer's disease	**0.44**	**0.34–0.58**	Age, race, SES, CCI, depression, stage	Reduced treatment
Griffiths 2014	Receipt	CCI 1	0.96	0.90–1.03	Age, ethnicity, SES, year, performance status, tumour factors	Reduced treatment, particularly with undetected comorbidity
		CCI ≥2	**0.74**	**0.66–0.82**		
		Undetected comorbidity 1	**0.81**	**0.73–0.90**		
		Undetected comorbidity ≥2	**0.38**	**0.30–0.49**		
Hawfield 2006	Receipt	CCI 1	0.80	0.3–2.4	Age, stage	Reduced treatment with higher comorbidity
		CCI ≥2	**0.20**	**0.0–0.9**		
Javid 2014	Receipt	CCI 0 (vs. CCI 3)	**2.60**	**1.7–4.0**	Age, race, rurality, year, treatment, tumour factors	Reduced treatment
Kimmick 2006	Receipt	CCI	0.94	0.82–1.08	Age, race, treatment, tumour factors	No difference
Kurian 2013	Receipt (within 12 months)	CCI 1	1.12	0.86–1.45	Age, race, SES, year, treatment, tumour factors	Reduced treatment with higher comorbidity, diabetes, neuropathy and heart disease
		CCI ≥3	**0.03**	**0.01–0.18**		
		Diabetes	**0.71**	**0.54–0.94**		
		Neuropathy	**0.53**	**0.31–0.89**		
		Heart disease	**0.38**	**0.26–0.56**		
Land 2012	Receipt	CCI 1	**0.52***	**0.47–0.56***	None	Reduced treatment
		CCI ≥3	**0.27***	**0.21–0.35***		
Lipscomb 2012	Receipt	CC ≥1	1.29	0.81–2.07	Age, race, SES, centre, tumour factors	No difference
Ma 2009	Receipt	CC 0 (vs. CC ≥2)	**2.50**	**1.2–5.4**	Age, tumour factors	Greater treatment with no comorbidity
Mandelblatt 2000	Receipt	ICED	1.11	0.90–1.36	Age, race, SES, year, region, centre, treatment, tumour factors	No difference
Mandelblatt 2010	Receipt chemo 'indicated'	CC (OARS) >2 (vs. 0–2)	0.80	0.4–1.6	Age, race, year, region, cognitive function, treatment, tumour factors	No difference
	Receipt chemo 'possibly indicated'	CC (OARS) >2 (vs. 0–2)	0.70	0.4–1.3		
Muss 1992	Receipt (within 4 months)	Comorbidity present	1.10	0.5–2.1	Age, ER status	No difference

Table 2 continued

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Nagel 2003	Receipt (within 9 months)	LN−: CCI ≥1	1.20	0.3–4.5	Age, caseload, tumour factors	No difference
		LN+: CCI ≥1	0.60	0.2–1.8		
Sabatino 2014	Guideline concordance	Mild type 2 DM	0.83	0.64–1.07	Age, ethnicity, SES	Reduced treatment with moderate/severe type 2 DM
		Moderate/severe type 2 DM	**0.58**	**0.36–0.94**	BMI, comorbidity, tumour factors	
Simon 2012	Receipt (within 2 months)	CCI	0.95	0.81–1.13	Age, ethnicity, SES, tumour factors	No difference
Srokowski 2009	Receipt (within 6 months)	Diabetes	**0.91**	**0.85–0.96**	Age, sex, ethnicity, SES, year, region, CCI, treatment, tumour factors	Reduced treatment
Wheeler 2012	Receipt (within 4 months)	Age 65–69: NCI Q1	0.95	0.58–1.56	Ethnicity, SES, organisational factors, year, timing of surg, tumour factors	Reduced treatment with higher comorbidity
		Age 65–69: NCI Q4	**0.32**	**0.17–0.60**		
		Age ≥70: NCI Q1	0.92	0.71–1.19		
		Age ≥70: NCI Q4	**0.59**	**0.44–0.77**		
Woodard 2003	Receipt	CCI ≥3	0.10*	0.01–1.81*	None	No difference
Zhu 2015	Receipt	CC ≥1	0.97*	0.75–1.24*	None	No difference

Bold indicates statistical significance at $p < 0.05$

BMI body mass index, *CC* comorbidity count, *CCI* Charlson comorbidity index, *chemo* chemotherapy, *CVD* cardiovascular disease, *DM* diabetes mellitus, *ER* estrogen receptor, *HTN* hypertension, *ICED* index of coexistent disease, *NCI Q1–4* National Cancer Institute index quartiles, *N/R* not recorded, *OR* odds ratio, *PR* progesterone receptor, *SES* socioeconomic status factors, *surg* surgery, *95% CI* 95% confidence interval

* OR/95% CI calculated from raw data

[a] OR for comorbidity measure compared with the absence of comorbidity or a comorbidity count/index score of 0 unless otherwise specified

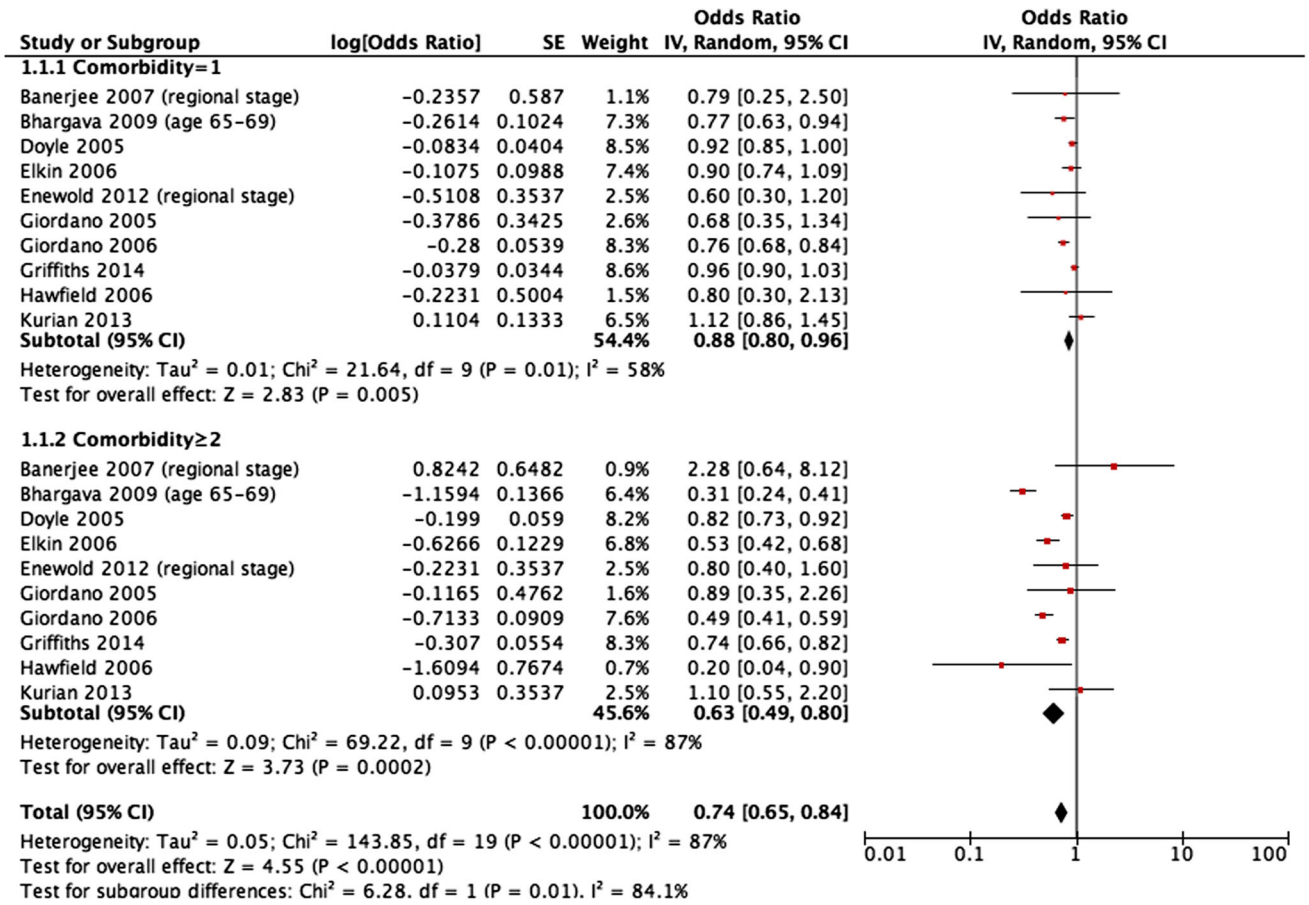

Fig. 1 Forest plot of receipt of chemotherapy: comorbidity versus no comorbidity

Regime

Thirteen studies considered differences in the chemotherapy regime received. The results were varied, depending on the comorbidity assessed and the comparison group. Overall, patients with comorbidity were less likely to receive combination anthracycline/taxane regimes (four studies [17, 48, 53, 63]). Taxanes alone (seven studies [17, 30, 48, 50, 53, 63, 69]) were used more frequently than combination or anthracycline-based regimes, particularly in patients with cardiac disease. Three out of four studies assessing CMF showed an increase in its use for patients with comorbidity [26, 49, 53]. Two studies reported on guideline concordance [32, 41] with respect to selection of standard regimes, with neither finding a difference pertaining to comorbidity.

Toxicity of chemotherapy

The measures used to assess toxicity were again heterogeneous in the 18 studies that considered this outcome (Table 4). Outcomes were synthesised into four subgroups: toxic events, febrile neutropenia, non-completion of treatment and hospital admission during chemotherapy.

Toxic events

Four studies examined grades 3–5 toxicities or adverse events [52, 61, 70, 73]. Two of these studies showed an increase in non-haematological toxicity for patients with comorbidity but no difference with regard to haematological toxicity [61, 73].

Febrile neutropenia

The occurrence of febrile neutropenia was analysed by six studies [22, 23, 40, 65, 67, 69], half of which demonstrated an increase in the odds of febrile neutropenia for patients with comorbidity [40, 65, 69].

Non-completion of treatment

Seven studies evaluated non-completion of expected treatment [16, 33, 39, 45, 55, 62, 70], with two showing a

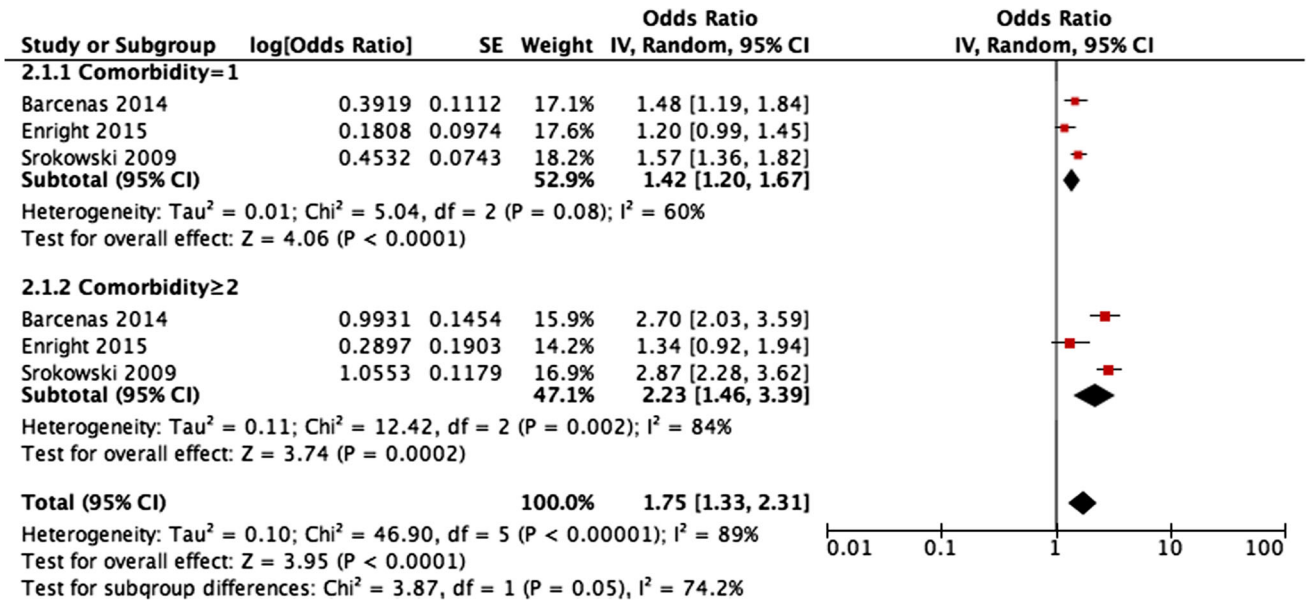

Fig. 2 Forest plot of hospital admission due to chemotherapy-associated toxicity: comorbidity versus no comorbidity

reduction in the odds of completion for patients with comorbidity [33, 45].

Hospital admission

Six studies reported on hospital admission during chemotherapy. All three studies which addressed all-cause hospitalisation during the course of chemotherapy treatment found an increase in the frequency of hospitalisation for patients with comorbidity [22, 30, 69].

Meta-analysis

Four studies [17, 30, 62, 69] assessed chemotherapy toxicity-associated hospital admission, three of which met inclusion criteria for meta-analysis (Fig. 2). The OR for chemotherapy toxicity-associated hospitalisation for patients with a comorbidity index score/count = 1 (compared with a score = 0) was 1.42 (95% CI 1.20–1.67), and 2.23 (95% CI 1.46–3.39) for a score ≥2. Heterogeneity was again high across the two subgroups ($I^2 = 89\%$).

Discussion

This review summarises the evidence regarding the use of chemotherapy for early breast cancer in patients with coexistent comorbidity. We report an overall reduction in the receipt of chemotherapy with any measure of comorbidity, with the odds of treatment progressively declining with increasing degree of comorbidity severity. This is in line with the literature reporting a reduction in the use of chemotherapy for comorbid patients with other malignancies, including non-Hodgkin's lymphoma [75], lung, colorectal and ovarian cancers [76]. Underuse of other breast cancer treatment modalities for comorbid patients has also been described, with studies reporting reduced receipt of primary breast surgery [37, 77], axillary dissections [29, 77–80], radiotherapy [20, 29, 37, 77, 78, 81–86] and reduced adherence to endocrine therapy [87].

There is ample evidence that breast cancer patients with comorbidities have poorer disease prognosis, which can be as important as stage in predicting survival [88, 89]. Comorbidity may act upon cancer mortality via direct processes associated with increased physiological burden of disease or accelerated cancer progression, or by indirect mechanisms related to its impacts on treatment uptake, quality and effectiveness [90]. The extent to which these mechanisms impact on survival is an important distinction, since treatment decisions are potentially amenable to intervention.

For elderly and comorbid patients with breast cancer, the decision to pursue or forgo curative intent chemotherapy is particularly complex, requiring consideration of projected non-cancer life expectancy in addition to the risks of relapse and treatment toxicity. Our increasing ability to accurately profile the biological features of breast tumours can help to discriminate patients who will derive the greatest benefit from chemotherapy from those in which it can be avoided [7]. While models such as Adjuvant! Online and PREDICT have been developed in order to aid treatment decisions and prognostication taking

Table 3 Change in quality of chemotherapy delivery in patients with comorbidity (selected results)

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Delay						
Fedewa 2010	90-day delay to receipt	CCI 1	**RR: 1.13**	**1.03–1.23**	Age, race, SES, year, region, treatment, tumour factors	More delays to receipt
		CCI ≥2	**RR: 1.32**	**1.10–1.60**		
Hershman 2006	Days to receipt	CCI 1 and ≥2	N/R	N/R	Age, race, SES, year, region, treatment, tumour factors	No difference
	≥90-day delay to receipt	CCI ≥2	1.00	0.7–1.5		No difference
O'Connor 2012	Treatment delay >7 days	CCI ≥1	**2.55**	**1.10–5.89**	Age, race, ECOG, BMI, comorbidities, treatment	More delays with comorbidity and HTN
		HTN	**2.51**	**1.02–6.20**		
Shayne 2006	Dose delay >7 days	CC ≥2	1.19*	0.50–2.81*	None	No difference
Simon 2012	>60-day delay to receipt	CCI	0.86	0.68–1.07	Age, ethnicity, SES, surg type	No difference
Dose						
Carroll 2014	Mean RDI <85%	Per comorbidity	1.05	0.86–1.28	Age, smoking status, BMI, treatment, tumour factors	No difference
Griggs 2003	First cycle dose reduction	CCI ≥1	0.50	0.18–1.36	Age, ethnicity, BMI, SES, year, treatment, tumour factors	No difference
	Dose proportion	CCI ≥1	N/R	N/R		No difference
	RDI	CCI ≥1	N/R	N/R		No difference
Griggs 2005	First cycle dose reduction <90%	CC ≥1	**1.99**	**1.09–3.62**	Age, year, treatment, LN status	More reductions
	Dose proportion	CC ≥1	N/R	N/R		No difference
Griggs (b) 2007	First cycle dose reduction <85%	CCI ≥1	1.16	0.60–2.25	Age, race, SES, BMI, region, regime	No difference
Griggs 2014	First cycle dose reduction <90%	CCI 1	1.31	0.59–2.94	Age, ethnicity, SES, BMI, centre, tumour factors	More reductions with higher comorbidity
		CCI ≥2	**2.65**	**1.11–6.33**		
Klepin 2014	Treatment modification	CCI ≥2	N/R	N/R	None	More modifications
O'Connor 2012	Unplanned dose reduction >10%	CCI ≥1	0.97	0.34–2.73	Age, race, ECOG, BMI, comorbidities, treatment	No difference
	RDI <85%	HTN	1.86	0.61–5.72		No difference
		CCI ≥1	1.74	0.78–3.89		
		HTN	1.44	0.64–3.25		
Shayne 2006	Dose reduction ≥15%	CC ≥2	2.27*	0.96–5.39*	None	No difference
	Planned dose reduction >10%	Renal disease	**21.16**	2.19–204.50	Age, body surface area	More reductions with renal disease
	RDI ≤85%	CC ≥2	2.25*	0.99–5.10*	None	
Shayne 2009	RDI ≤ 85%	CCI 2-4	2.16*	0.59-7.82*	None	No difference
Regime						

Table 3 continued

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Barcenas 2014	Anthracycline (AC)	CCI 1	0.85*	0.72-1.01*	None	Greater use of taxanes and less use of anthracyclines with higher comorbidity
	Taxane (TC)	CCI ≥2	**0.76***	**0.59–0.99***		No difference
	Combined anthracycline/taxane (TAC or ACP)[b]	CCI 1	1.16*	0.93–1.44*		
		CCI ≥2	**1.48***	**1.09–2.00***		
		CCI 1	1.07*	0.91–1.27*		
		CCI ≥2	1.02*	0.80–1.31*		
Bowles 2012	Anthracycline ± trastuzumab	CCI 1	**0.59***	**0.51–0.69***	None	Reduced treatment with anthracycline ± trastuzumab
		CCI ≥3	**0.25***	**0.19–0.32***		
Doyle 2005	Anthracycline (doxorubicin)	CCI 1	**0.83**	**0.70–0.98**	Age, year, comorbidities, treatment, stage	Reduced treatment with anthracyclines
	CMF	CCI ≥2	**0.58**	**0.45–0.75**		No difference
		Heart disease	**0.78**	**0.68–0.90**		
		CCI 1	0.95	0.82–1.11		
		CCI ≥2	0.95	0.77–1.17		
		Heart disease	1.20	0.56–1.36		
Du 2015	Anthracycline (AC)	CCI 1	0.89*	0.79–1.00*	None	Reduced treatment with anthracyclines
	CMF	CCI ≥3	**0.37***	**0.27–0.51***		Increased use of CMF with higher comorbidity
		CCI 1	1.08*	0.92–1.26*		
		CCI ≥3	**1.50***	**1.09–2.05***		
Enright 2015	Anthracycline	CCI 1	**1.34***	**1.10–1.64***	None	Greater use of anthracyclines and less use of taxanes with mild comorbidity
	Taxane (docetaxel or paclitaxel)[b]	CCI ≥2	1.46*	0.98–2.18*		
		CCI 1	**0.72***	**0.59–0.88***		
		CCI ≥2	0.69*	0.46–1.04*		
Freedman 2014	Non-standard regime	CCI ≥2	1.37	0.88–2.14	Ethnicity, SES, year, region, tumour factors	No difference
Griggs (a) 2007	Non-standard regime	CCI ≥1	0.93	0.53–1.64	Age, ethnicity, SES, region, unknown ER/PR status	No difference
Jitawatanarat 2014	Combined anthracycline/taxane (AC-TH)	Cardiac history	**0.08***	**0.01–0.72***	None	Greater use of taxanes and less use of combined regime with cardiac history
	Taxane (TCaH or TCyH)[b]	HTN	0.64*	0.33–1.24*		
		Diabetes	1.12*	0.40–3.14*		
		Cardiac history	**11.89***	**1.40–101.2***		

Table 3 continued

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
		HTN	1.57*	0.81–3.07*		
		Diabetes	0.89*	0.32–2.51*		
Kadakia 2015	CMF	CCI ≥1	**1.17**	**1.05–1.30**	Age, race, SES, year, treatment, tumour factors	Greater use of CMF with comorbidity
		Renal failure	0.92	0.63–1.35		
Kaplan 2012	Anthracycline	Type 2 diabetes	0.82*	0.50–1.34*	None	No difference
	Taxane	Type 2 diabetes	1.22*	0.75–2.01*		
Kurian 2013	Anthracycline	Diabetes	0.70	0.46–1.05	Age, race, comorbidities, treatment, tumour factors	Reduced use of anthracyclines with heart disease. Reduced use of taxanes with neuropathy
	Taxane	Heart disease	**0.24**	**0.14–0.41**		
	Combined anthracycline/taxane	Neuropathy	**0.45**	**0.22–0.89**		
	CMF	CCI 1	**0.65**	**0.47–0.90**		
		CCI ≥3	0.55	0.04–7.09		
		Diabetes	**0.66**	**0.46–0.94**		
		Diabetes	**4.09**	**1.59–10.5**		Reduced use of combined regime with diabetes
		Heart disease	**10.2**	**3.64–28.6**		Greater use of CMF with diabetes and heart disease
Rocque 2012	Combined anthracycline/taxane (AC-TH)	Cardiac disease	**0.17***	**0.04–0.84***	None	Greater use of taxanes and less use of combined regimes with cardiac disease. No difference with diabetes and HTN
	Taxane (TCaH)	Diabetes	0.42*	0.15–1.21*		
		HTN	0.61*	0.33–1.14*		
		Cardiac disease	**8.75***	**2.16–35.37***		
		Diabetes	2.80*	0.98–7.99*		
		HTN	1.12*	0.55–2.30*		
Srokowski 2009	Anthracycline	Diabetes	**0.78**	**0.71–0.87**	Age, sex, ethnicity, SES, CCI, year, region, surg type, tumour factors	Reduced treatment with both anthracyclines and taxanes
	Taxane	Diabetes	**0.86**	**0.75–0.99**		

Bold indicates statistical significance at $p < 0.05$

AC doxorubicin and cyclophosphamide, *ACP* doxorubicin, cyclophosphamide and paclitaxel, *AC-TH* doxorubicin, cyclophosphamide, paclitaxel and trastuzumab, *BMI* body mass index, *CC* comorbidity count, *CCI* Charlson comorbidity index, *CMF* cyclophosphamide, methotrexate and fluorouracil, *ECOG* Eastern Cooperative Oncology Group performance status, *ER* estrogen receptor, *HTN* hypertension, *LN* lymph node, *N/R* not recorded, *OR* odds ratio, *PR* progesterone receptor, *RDI* relative dose intensity, *RR* relative risk, *SES* socioeconomic status factors, *surg* surgery, *TAC* docetaxel, doxorubicin and cyclophosphamide, *TC* docetaxel and cyclophosphamide, *TCaH* docetaxel, carboplatin and trastuzumab, *TCyH* docetaxel, cyclophosphamide and trastuzumab, *95% CI* 95% confidence interval

* OR/95% CI calculated from raw data

[a] OR for comorbidity measure compared with the absence of comorbidity or a comorbidity count/index score of 0 unless otherwise specified

[b] Raw data for more than one regime were combined for this analysis

certain tumour characteristics into account, none consider an objective assessment of comorbidity.

While reasons for the underuse of chemotherapy in patients with concomitant comorbidity are likely to be multifaceted, the risk of treatment-related toxicity is a commonly cited concern [52, 64, 91]. Toxicity can potentially shorten remaining life expectancy so as to cancel any gains incurred by therapy. We report an approximate doubling of the odds of hospitalisation for chemotherapy-associated toxicity from a comorbidity severity score/count of one to $\geq$2. There was also an increase in the odds of all-cause hospitalisation during the course of chemotherapy treatment for comorbid patients. This may be due to the exacerbation of pre-existing conditions by chemotherapy, reduced physiological reserve, or even a lower threshold for admission in such patients.

While clinical trials provide the gold standard evidence on chemotherapy effectiveness and tolerance, their 'ideal' participants can limit their generalisability to the wider patient population. Some observational studies have attempted to determine whether treatment still has a positive impact on outcomes for patients with comorbidity, despite their potential increased risk of toxicity. Such studies performed in patients with colon [92] and prostate [93] cancer have demonstrated a survival advantage for comorbid patients treated with chemotherapy over similar patients who were not, suggesting that some patients have had potentially curative treatment unnecessarily modified.

For comorbid patients who did receive chemotherapy, our review shows that the quality of treatment was highly variable. The adverse impact on survival of late initiation of adjuvant chemotherapy has been demonstrated in several studies [46, 94, 95]. Delays to the commencement of chemotherapy in comorbid patients may be due to post-surgical complications or a requirement for medical investigations and optimisation prior to adjuvant treatment. Encouragingly however, only one of three studies addressing this outcome in our review found a delay to the initiation of chemotherapy in comorbid patients.

In order to achieve maximal benefits in terms of disease-free and overall survival from adjuvant chemotherapy, it is also important to maintain planned dose intensity [96, 97]. Reassuringly, all seven studies addressing dose proportion or RDI in our review showed no difference for patients with comorbidity. However, two out of four studies did report greater odds of a first cycle dose reduction in patients with comorbidity, signifying intentional physician prescribing rather than a response to toxicity.

A variety of chemotherapy regimens were evaluated by the studies in our review and comparisons were heterogeneous. Overall, patients with comorbidity were less likely to receive combination anthracycline/taxane regimes, which have been shown in several reviews to improve disease-free and overall survival in comparison with either agent alone in the adjuvant setting [98–100]. Comorbid patients were more likely to receive CMF, perhaps due to the perception that CMF is a less toxic regime. Unfortunately, as the studies included in this review only examined broad patterns of chemotherapy use, it was not possible to examine treatment patterns in relation to specific disease stage or subtype.

While this review demonstrates that comorbidity has an overall adverse impact on the use, quality and tolerance of chemotherapy, a wide variation in the definition of comorbidity used does make it difficult to formulate inter-study comparisons. At its most basic, comorbidity is the presence of health-related conditions that coexist with a primary disease of interest [101]. A range of methods have been used to classify an individual's level of comorbidity, including simple counts of conditions, organ-based systems and indices weighted to predict mortality [102]. Conceivably, individual conditions and particular combinations of conditions will have differing impacts on the uptake and tolerance of chemotherapy. Unfortunately however, very few studies in this review considered the impact of individual comorbid conditions on the outcomes of interest, making it difficult to shape such conclusions.

A majority of studies included in this review were retrospective in nature and used multiple regression modelling in an attempt to control for measured confounding biases. While the meta-analyses were restricted to studies which controlled for age and stage of disease, there was still significant heterogeneity. Many studies took advantage of population-based cancer registries linked with an administrative database, such as the SEER-Medicare database. While these data sources are a practical way to measure the impact of comorbidity on cancer outcomes in a large population, the data are collected for hospital billing rather than research purposes. As such, the scope of questions which can be posed about chemotherapy treatment is constrained by an inability to address important potential confounding influences, including performance status, cognitive function, lymphovascular invasion and Her2 expression. SEER records also largely exclude those younger than 65 years, restricting any assessment of the impact of comorbidity on outcomes in younger cancer patients.

While breast cancer survival has improved in recent decades due to earlier diagnosis and improved adjuvant therapy [103], this has been largely experienced by patients without comorbidity [104, 105]. Comorbidity continues to pose a significant challenge to the traditional sub-specialty model of breast cancer treatment. Breast cancer guidelines essentially adopt a 'single disease' approach to management and offer little guidance to cancer clinicians dealing with patients who have complex health needs. Novel

Table 4 Toxicity of chemotherapy delivery in patients with comorbidity (selected results)

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Toxic events						
Klepin 2014	Grades 3–5 adverse event	CC (OARS)	0.97	0.86–1.09	None	No difference
Nuzzo 2008	Grades 3–4 toxicity (haem)[b]	CCI 2–3 (vs. 0–1)	0.91*	0.33–2.52*	None	Increased non-haematological toxicity with higher comorbidity
	Grade 3–4 toxicity (non-haem)[b]	CCI ≥3 (vs. 0–1)	0.72*	0.24–2.16*		
		CCI 2–3 (vs. 0–1)	2.36*	0.59–9.36*		
		CCI ≥3 (vs. 0–1)	**4.21***	**1.03–17.29***		
Von Minckwitz 2015	Grades 3–5 toxic event	CCI 0 (vs. 1–2)	0.84	0.42–1.68	Age, BMI, ECOG, no. co-medications, geriatric scores, blood results, stage	No difference
Zauderer 2009	Grades 3–4 toxicity (overall)	CCI ≥1	**2.15**	**1.04–4.46***	Age, haemoglobin, completion of treatment	Increased non-haematological & overall toxicity
	Grades 3–4 toxicity (haem)	CCI ≥1	1.21	0.47–3.09*		
	Grades 3–4 toxicity (non-haem)	CCI ≥1	**2.97**	**1.30–6.80***		
Febrile neutropenia						
Carroll 2014	Febrile neutropenia	Per comorbidity	0.98	0.78–1.24	Age, smoking status, BMI, treatment, tumour factors	No difference
Chan 2012	Febrile neutropenia	CC ≥1	1.20	0.52–2.77	None	No difference
Griggs 2005	Hospital admission (febrile neutropenia)	CC ≥1	**3.06**	**1.15–8.18**	Age, year, blood results, treatment	Increased admission for febrile neutropenia
Schwenkglenks 2011	Grade 4 neutropenia	Vascular	**2.29**	**1.25–4.20**	Age, weight, blood results, treatment	Increased neutropenia
Shayne 2009	Febrile or severe neutropenia	CCI 1	0.64*	0.32–1.25*	None	No difference
						More anaemia
						No difference
		CCI 2–4	0.72*	0.20–2.70*		
	Anaemia	CCI ≥1	**2.17***	**1.12–4.19***		
	Thrombocytopenia	CCI ≥1	1.27*	0.49–3.29*		
Srokowski 2009	Hospital admission (neutropenia)	Diabetes	**1.22**	**1.03–1.45**	Age, sex, ethnicity, SES, comorbidity	Increased admission for neutropenia with comorbidity and diabetes
		CCI ≥2	**1.67**	**1.15–2.42**	Year, region, treatment, tumour factors	
Hospital admission						
Barcenas 2014	Hospital admission (chemo-associated)	CCI 1	**1.48**	**1.19–1.84**	Age, ethnicity, SES, year, region, treatment, tumour factors	Increased chemo-associated hospital admission
		CCI ≥2	**2.70**	**2.03–3.59**		

Table 4 continued

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Carroll 2014	Hospital admission (all-cause)	Per comorbidity	**1.22**	**1.04–1.43**	Age, smoking status, BMI, treatment, tumour factors	Increased admission
Enright 2015	Hospital admission (all-cause)	CCI 1	**1.45**	**1.21–1.74**	Age, SES, region, treatment, stage	Increased all-cause hospital admission
	Hospital admission (chemo-associated)	CCI ≥2	**2.04**	**1.41–2.96**		No difference
		CCI 1	1.20	0.99–1.45		
		CCI ≥2	1.34	0.92–1.94		
Griggs 2005	Hospital admission (febrile neutropenia)	CC ≥1	**3.06**	**1.15–8.18**	Age, year, blood results, treatment	Increased admission for febrile neutropenia
O'Connor 2012	Hospital admission (chemotoxicity)	CCI ≥1	2.17	0.99–4.75	Age, race, ECOG, BMI, comorbidity, treatment	Increased admission with HTN
		HTN	**2.87**	**1.22–6.72**		
Srokowski 2009	Hospital admission: all-cause	Diabetes	**1.32**	**1.19–1.46**	Age, sex, ethnicity, SES, comorbidity	Increased hospital admission for all reasons with comorbidity and diabetes
	Chemo toxicity	CCI ≥2	**2.75**	**2.21–3.42**	Year, region, treatment, tumour factors	
	Infection/fever	Diabetes	**1.38**	**1.23–1.56**		
	Neutropenia	CCI ≥2	**2.87**	**2.28–3.62**		
	Anaemia	Diabetes	**1.43**	**1.20–1.70**		
		CCI ≥2	**2.52**	**1.84–3.44**		
		Diabetes	**1.22**	**1.03–1.45**		
		CCI ≥2	**1.67**	**1.15–2.42**		
		Diabetes	**1.24**	**1.05–1.47**		
		CCI ≥2	**3.28**	**2.48–4.34**		
Non-completion of chemotherapy						
Barcenas 2012	Completion of ≥4 cycles	CCI 1	1.01	0.86–1.19	Age, race, SES, year, region, treatment, tumour factors	No difference
		CCI ≥2	1.21	0.93–1.58		
Garg 2009	Completion of treatment	CCI ≥1	**0.007***	**0.001–0.15***	None	Reduced completion
Griggs 2003	Time ratio	CCI ≥1	N/R		Age, ethnicity, BMI, SES, treatment, LN status	No difference
Hershman 2005	Completion of expected treatment	CCI 1	0.62*	0.35–1.13*	None	Reduced completion with higher comorbidity
		CCI ≥2	**0.48***	**0.23–0.99***		
Lipscomb 2012	Completion of planned treatment	CC ≥1	0.53	0.26–1.09	Race, marital status	No difference
O'Connor 2012	Early treatment discontinuation	CCI ≥1	1.97	0.88–4.41	Age, race, ECOG, BMI, comorbidities, treatment	No difference
		HTN	1.64	0.72–3.74		

Table 4 continued

Studies	Outcome reported	Comorbidities[a]	OR	95% CI	Adjustment variables	Conclusions
Von Minckwitz 2015	Early treatment discontinuation	CCI 0 (vs. 1–2)	1.22	0.61–2.46	Age, BMI, ECOG, no. co-medications, geriatric scores, blood results, stage	No difference

BMI body mass index, *CC* comorbidity count, *CCI* Charlson comorbidity index, *ECOG* Eastern Cooperative Oncology Group performance status, *haem* haematological, *HTN* hypertension, *OARS* older Americans resources and services multidimensional functional assessment, *OR* odds ratio, *SES* socioeconomic status factors, *95% CI* 95% confidence interval

Bold indicates statistical significance at $p < 0.05$

* OR/95% CI calculated from raw data

[a] OR for comorbidity measure compared with the absence of comorbidity or a comorbidity count/index score of 0 unless otherwise specified

[b] Raw data for more than one regime were combined for this analysis

models of care which incorporate a greater diversity of expertise and coordination within oncology systems are required. There is a need to conduct high-quality prospective chemotherapy trials dedicated to comorbid patients with breast cancer in order to comprehensively examine efficacy/toxicity and develop more tolerable regimes/dose schedules which maintain efficacy. The development of a comprehensive decision algorithm synthesising breast cancer-specific and competing cause mortality would also be a highly valuable resource. Such a tool could facilitate and enhance patient–physician communication by weighing up the potential risks and benefits of chemotherapy when making treatment decisions in patients with comorbidity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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