Comorbidity-dependent adherence to guidelines and survival in breast cancer—is there a role for guideline adherence in comorbid breast cancer patients? A retrospective cohort study with 2137 patients

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Abstract
In the treatment of breast cancer, decisions on adjuvant treatment reflect individual patient characteristics like age and comorbidity. This study assessed the association between adherence to guidelines for adjuvant treatment and survival while taking into account age at diagnosis and comorbidities. We collected the Charlson comorbidity index at baseline for 2179 women treated for primary breast cancer from 1992 to 2008 who participated in a German retrospective multicenter cohort study. We assessed subsequent adjuvant therapy guideline adherence and survival in relation to baseline comorbidities. Guidelines for adjuvant chemotherapy and radiotherapy were more often violated in patients with higher Charlson score. Patients with higher Charlson scores received chemotherapy and radiotherapy less often and had higher rates of mastectomy. Irrespective of comorbidity (Charlson score 0, 1-2, ≥3), patients with 100% guideline-adherent adjuvant treatment showed better overall and disease-free survival (DFS) compared to patients with guideline violations (GVs). Controlling for age, comorbidity and tumor characteristics, the hazard ratio for at least one GV was 1.65 (95% confidence interval [CI]: 1.33-2.07) for overall survival and 1.84 (95% CI: 1.53-2.22) for DFS. Guideline-adherent treatment was significantly less frequent in comorbid patients, although guideline adherence was strongly associated with improved survival, irrespective of severity, and number of comorbid diseases.

1 | INTRODUCTION
Breast cancer is the most common malignancy in women in industrialized countries, occurring with an annual frequency of more than 75 000 new cases in Germany. Because of the sequelae and the enormous health-economic impact of the disease, multiple national and international treatment guidelines have been established following decades of intensive clinical research. These guidelines aim to increase the quality of breast cancer care and thus improve the outcome for breast cancer patients. However, guidelines usually do not account for comorbidity. Hence, there is an urgent need for more research on the implementation of guidelines in the treatment of daily-routine patients, who might differ substantially from members of more selective and therefore potentially biased study cohorts.

There is strong evidence demonstrating that age and comorbidities are important predictors of guideline adherence in breast cancer treatment. However, the role of comorbidity in guiding adjuvant treatment selection in breast cancer patients has not been adequately addressed. In this study, we assessed the association between guideline adherence and survival while taking into account age at diagnosis and comorbidities.
cancer. This association has also been described for several other malignancies and their corresponding guidelines. In fact, there is a complex association between age, patient- and physician-related factors on the one hand, and guideline-adherent treatment on the other hand, which influences survival parameters. This association may help explain why guideline adherence decreases rapidly with age and why non-cancer-related mortality is rising. Increasing life expectancy and rising breast cancer incidence in elderly women therefore pose a challenge to clinical oncologists who have to find optimal treatment plans in the face of sometimes severe comorbidities. It is an open question whether guideline adherence can improve the clinical outcome specifically for this patient group. Age might only be a surrogate parameter for comorbidities indicating that guideline adherence might be more dependent on biologic age potentially defined by health condition instead of numerical age. When reporting about the association between survival and comorbidities in breast cancer, Kimmick et al. recently suggested to include guideline adherence among the covariates.

For a subsample of patients originally included in the Brenda study on effects of guideline adherence, we retrospectively collected data from clinical files to calculate the validated Charlson comorbidity index (see Table 1) at time of surgery. The aim of this study is to investigate the association between baseline comorbidity, age, and the administration of surgery as well as three different adjuvant treatment modalities (chemotherapy, radiotherapy, and endocrine therapy). We also strived to investigate the impact of guideline adherent adjuvant treatment on survival in comorbid patients defined by the Charlson comorbidity index.

2 MATERIAL AND METHODS

In this retrospective single-center cohort study we analyzed data from 2137 women with primary breast cancer diagnosed or treated in Germany at the Department of Gynaecology and Obstetrics at the University of Ulm between 1992 and 2008. These women are a subgroup of the cohort of 10,897 women recruited in the Brenda trial from Ulm and 16 other participating breast cancer centers.

The Brenda documentation system included a retrospective chart review to abstract TNM stage, histologic subtype, grading, lymphatic and vascular invasion, estrogen, progesterone, and Her2 expression, date of diagnosis, and all adjuvant therapies. Data on therapies, including surgery (date of surgery, breast conserving therapy, mastectomy, sentinel-node biopsy, and axillary lymph node dissection), adjuvant systemic chemotherapy, adjuvant endocrine therapy, and detailed information on adjuvant radiotherapy were also collected.

The study was approved by the ethics review board of the university medical hospital Ulm. The inclusion criterion was histologically confirmed invasive breast cancer. The exclusion criteria were carcinoma in situ, primary metastatic disease, bilateral breast cancer, primary occult disease, phylloides tumor, incomplete follow-up, unknown Her2 status or hormone receptor status (HR status), or missing data on variables used as covariates in the survival analyses. In addition, we excluded patients with less than 1 year of follow-up.

Active follow-up was performed for all patients until December 31, 2012. During follow-up, data on first recurrences, secondary primary tumors, and date and cause of death were obtained. Questionnaires were sent to the physicians involved in the follow-up care, to local death registers, and to patients to determine the recurrence and vital status of the patients.

In 2014, we reviewed the preoperative anaesthesiologic examination for 2520 women of the Brenda study cohort—all of whom treated at the university hospital Ulm, Germany—to collect detailed information on comorbidities at baseline. The Somatic diseases were coded according to the Charlson Comorbidity Index which assigns weights to diseases depending on their associated risk of dying. We considered groups with a Charlson score of 0 (no comorbidity), 1-2 ("mild somatic comorbidity") and ≥3 ("severe somatic comorbidity"). While potentially relevant, no information on lifestyle factors affecting functional status could be ascertained.

For all patients, the definition of guideline-adherent adjuvant treatment was retrospectively defined according to the same German national consensus guideline (S3 guideline, 2008) for the decision of loco-regional treatment (surgery and radiotherapy), chemotherapy, and endocrine therapy. Wolters et al. demonstrated that the treatment recommendations within international guidelines are identical and differ only marginally in adjuvant endocrine therapy. Omission of any of the suggested adjuvant treatment was classified as noncompliance to the suggested adjuvant therapy, resulting in one or more guideline violations (GV) for each patient.

2.1 Statistical analysis

Descriptive analyses were performed separately for the groups defined by the Charlson comorbidity index (0, 1-2, 3 or greater). P-values for the comparisons between the three groups are based on chi-squared tests or the Kruskal-Wallis test; P-values will be presented but should be interpreted with some caution as no adjustment for multiplicity was done. The Kaplan-Meier method and log-rank tests were used to compare overall survival (OS) and disease-free survival (DFS) between the three Charlson score groups in univariate analyses.

In multivariate survival analyses for the same end points (OS and DFS), we performed Cox-regression to estimate hazard ratios (HRs)
and their confidence intervals (CIs) for the risk factor of at least one GV. Guideline-adherence requires the patient to stay alive until recommended adjuvant treatments can commence. By limiting our sample to women with follow-up of at least 1 year, we mitigated the risk of immortal time bias favoring women without GV.

All of the regression models were adjusted for age at diagnosis (in years), tumor size (4 categories), grading (3 categories), nodal status (0, 1-3, or 4+ positive nodes), menopausal status (binary), year of diagnosis, and baseline comorbidities. Comorbidities were measured using the scale of the American Society of Anesthesiologists (ASA, score 3 or greater), the scale of the New York Heart Association (NYHA, class 3 or higher), and Charlson index group (3 categories). The assumption of proportional hazards was checked by examining complementary log-log plots for linearity and parallelity of the lines for Charlson index groups.

In addition, we performed a logistic regression to predict guideline adherence using age and Charlson index group as covariates. All analyses were carried out in R (Version 3.3.0), using the survival package.

### RESULTS

From the complete Brenda cohort of 10,897 women recruited from 17 breast cancer centers from 1992 to 2008, anestesiologic reports could be retrospectively assessed for 2,520 patients, all of whom treated at the university hospital Ulm. Of these, 383 patients were...
excluded. Of these, 47 had a T-status that was either 0 or missing; 53 had missing grading, 8 had bilateral tumors, and 48 had follow-up of less than 1 year. Data for some of the covariates used in our analyses were missing for the remaining 234 patients. The final cohort consisted of 2137 patients with histologically confirmed invasive breast cancer (see Table 2).

Median follow-up time was 5.7 years with a maximum of 12.7 years. Stratified by Charlson index, patients with index 0 had a median follow-up time of 5.9 years, those with index 1-2 had 5.2 years median follow-up, and those with index 3 or more had 4.6 years median follow-up.

3.1 Demographic information and tumor characteristics

Patients with higher Charlson index were significantly older at baseline (P<.0001; see Table 3): 1551 patients (72.6%) had a Charlson index of 0 (median age: 56.8, range 26-89), 496 patients (23.2%) had an index of 1-2 (median age: 66.1, range 29-94), and 90 (4.2%) had a Charlson index of 3 or more (median age: 72.3, range 37-93). In the same vein, the proportion of postmenopausal women was significantly higher (P<.0001) in groups with higher Charlson index: 65.6% (index 0) vs 83.5% (index 1-2) vs 96.7% (index 3 or more).

Charlson groups differed significantly (P<.001) in the proportion of T-status: Although 53.6% had T-status 1 in the group with Charlson index 0, this proportion was 46.2% for the group with Charlson index 1-2, and dropped to 36.7% for the group with Charlson index 3 or more. Patients with higher Charlson score had significantly less often (P<.03) endocrine nonresponsive cancers: 14.7% (index 0) vs 12.7% (index 1-2) vs 12.2% (index 3 or more).

3.2 Adjuvant treatment and guideline adherence

Adjuvant treatment differed significantly between Charlson index groups: Groups with higher index received chemotherapy less often (P<.0001) with proportions 53.3% (index 0) vs 36.1% (index 1-2) vs 25.6% (index 3 or more). The same holds for radiotherapy (P<.0001) where the proportion dropped from 85.7% (index 0) to 77.2% (index 1-2) to 57.8% (index 3). Contrary, higher Charlson index groups had mastectomy more often (P<.001) with proportions 21.4% (index 0) vs 25.2% (index 1-2) vs 38.9% (index 3 or more).

When Charlson index was higher, guidelines for adjuvant treatment were significantly more often violated with respect to radiotherapy and chemotherapy (both P<.001): Despite indication, radiotherapy was omitted in 6.2% (index 0) vs 10.7% (index 1-2) vs 24.4% (index 3 or more). Similarly, 5.7% (index 0) vs 9.3% (index 1-2) vs 13.3% (index 3 or more) did not receive chemotherapy even though it was indicated. For radiotherapy, Charlson index group predicted GVs even after adjusting for age (P=.004). In contrast, it ceased to be a significant predictor for chemotherapy GVs when adjusting for age (P=.9).

Surgery and endocrine under therapy did not show significant differences between the Charlson index groups (P>.05; see Table 4).

3.3 Survival

Univariate analyses showed that comorbidities as classified by the Charlson index were strongly associated with worse OS as well as worse DFS (both P<.0001).

After stratification for Charlson index group, univariate analyses indicated a significant advantage for overall guideline adherence (0 GVs vs 1 or more violations) for OS as well as for DFS (both P<.0001). This advantage could be confirmed in each Charlson group separately: Even for patients with severe somatic comorbidities (Charlson index 3 or more), those with no GVs showed better OS and DFS than those with at least 1 violation (both P<.0001; see Figure 1).

For OS, multivariate analyses found an adjusted HR of 1.51 (CI: 1.19-1.90) for at least one GV (P=.001). For DFS, the adjusted HR was 1.71 (CI: 1.41-2.07) for at least one GV (P<.0001; see Figure 2).

4 DISCUSSION

Our data demonstrate a strong association between age, comorbidities and guideline adherence. Our results support that for radiotherapy, guideline adherence is not just linked to age, but independently to the presence of comorbid conditions as well. For guideline adherence with respect to the remaining adjuvant treatment modalities, this may imply that their association with age is at least partially due to the effect of comorbidities. However, the retrospective nature of our study makes it difficult to disentangle the precise relationship between age, comorbidities, and guideline adherence.

**TABLE 4** Number and percentage of guideline violations (GV) among groups with Charlson index 0 vs 1-2 vs 3 or more, stratified for all adjuvant treatment modalities (surgery, chemotherapy, and radiotherapy)

| Charlson 0 | Charlson 1-2 | Charlson >3 |
|-----------|-------------|-------------|
| % N       | % N         | % N         |
| ≥1 GV     | 32.0 497/1551 | 34.5 171/496 | 42.2 38/90  | .1 |
| GV endocrine therapy | 9.9 154/1551 | 8.5 42/496 | 11.1 10/90  | .6 |
| GV radiotherapy | 6.2 96/1551 | 10.7 53/496 | 24.4 22/90  | <.0001 |
| GV surgery | 17.3 269/1551 | 14.7 73/496 | 13.3 12/90  | .3 |
| GV chemotherapy | 5.7 88/1551 | 9.3 46/496 | 13.3 12/90  | <.001 |
FIGURE 1  Overall survival and disease-free survival with 95% confidence interval for patients who received (vs those who did not receive) 100% guideline-adherent adjuvant treatment, as stratified by Charlson index group (0, 1-2, and 3 or more)
In particular, we cannot fully infer the motivation for GVs either on the side of the physician or on the side of the patient. Currently, no guidelines exist for clear comorbidity-dependent contraindications against adjuvant treatment. Therefore, weighing the benefits of adjuvant treatment against the risk of compromising an organ that is already compromised due to comorbidity was at the discretion of the attending physician. The available documentation did not allow us to systematically identify whether avoidance of adjuvant treatment was specifically due to health concerns from pre-existing comorbidities.

We observed two strong associations with clinical outcome in breast cancer: Comorbidities were associated with significantly inferior outcome parameters. Importantly, guideline adherence proved to be an independent factor in predicting clinical outcome. Even in the presence of severe comorbidities, there is an association between guideline adherence and improved outcome parameters. There may
be physician-related factors that prevented patients from obtaining guideline-adherent treatment, and it is possible that patients were deemed unsuitable for strict guideline-adherent treatment because of comorbidities. This data therefore indicates the importance of adjuvant treatment in comorbid patients and underlines the need of individualized multi-disciplinary decision-making in tumor boards. The implementation of comorbidity assessments into upcoming guideline recommendations could help to improve guideline adherence.

Best to our knowledge, there are only few studies investigating the association between comorbidities, guideline adherence, and outcome.8 One of the major problems is the classification of comorbidities, which is the most important reason why we decided to use the validated Charlson score instead of nonvalidated scores like ASA or NYHA score. Kimmick et al.12 used the ACE-27, a tool especially developed for cancer patients to categorize and evaluate presence and severity of comorbidities. While the Charlson score used in this analysis does not reflect the severity of comorbidities in full depth, Kallogjeri et al.23 compared ACE-27 with the Charlson score and concluded that the latter is able to provide unique prognostic information. Likewise, the more encompassing Elixhauser score proved to be slightly superior to the Charlson score in contributing to the prediction of 2- and 3-year OS after colorectal cancer.23,24 However, in a direct comparison of several comorbidity measures, Baldwin et al.25 conclude that, minor advantages of some scores over others notwithstanding, Charlson is fairly robust in accounting for non-cancer death. The authors recommend choosing one among the validated measures based on availability of the required information.

Several other studies investigated the impact of comorbidities on survival in breast cancer patients,26-28 but none of these studies present data on guideline adherence.

Randomized controlled trials are generally viewed as the gold standard for the evaluation of therapy regimens. However, comorbid patients are often underrepresented in the selected patient cohorts due to strict inclusion criteria. Results of these trials are the foundation of evidence based guidelines. The adoption and impact of guideline adherent treatment for routine patients with a higher prevalence of comorbidities can therefore only be investigated in observational studies. The main advantage of the Brenda cohort, which represents the daily routine of patients observed in clinical practice, is that it avoids any selection bias that occurs in clinical trials. As such, the Brenda cohort is also associated with greater comorbidities, is older, and includes several patients who declined adjuvant treatment modalities.5

The methodological difficulty associated with retrospective data collection in all of these studies, including this study, only allows us to draw associations between guideline-adherent treatment and favorable outcome parameters; drawing causal conclusions concerning survival parameters would only be appropriate if treatment allocations were randomized and prospective. However, randomization concerning guideline-adherent treatment was not possible because we could not randomly assign guideline-adherent and nonguideline-adherent therapeutic regimes to patients.

In this retrospective study, there were confounding factors affecting both treatment and outcome parameters. To reduce this problem, our analyses controlled for the most important prognostic factors (age, affected lymph nodes, grade, hormone receptor status, menopause status, year of diagnosis, tumor size, erbB-2-status, and comorbidities). Comorbidities are likely one of the most important clinical factors preventing patients from guideline-adherent treatment, which may substantially influence prognosis.29,30 In this specific cohort, all patients were treated in a specialized and certified interdisciplinary breast cancer center, in which an interdisciplinary tumor board is a requirement for certification. Of course, several other factors influence guideline-adherence in breast cancer, such as patient beliefs and education, access to medical resources, health care services obtained, or urban vs rural setting.31

Aside from external influences, we believe that comorbidities are the most important clinical factor preventing patients from guideline adherent adjuvant treatment. However, guideline adherent adjuvant treatment is associated with a substantial improvement in survival parameters even in comorbid patients. Individualized and multi-disciplinary decision-making and strict indications when avoiding guideline adherent therapies is crucial.

5  CONCLUSION

Guideline-adherent treatment appeared less frequent in comorbid breast cancer patients, even though guideline adherence was strongly associated with improved survival, irrespective of severity, and number of comorbid diseases.

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