Comorbidity as a Mediator of Survival Disparity Between Younger and Older Women Diagnosed With Metastatic Breast Cancer

Su Yon Jung, Margaret Rosenzweig, Faina Linkov, Adam Brufsky, Joel L. Weissfeld, Susan M. Sereika

Abstract—The presence of comorbidity becomes increasingly important for its prognostic effect on survival in breast cancer patients with advancing age. This study aimed to evaluate the role of comorbidities including hypertension as a mediator of disparity in survival after metastasis diagnosis between younger (≤51 years) and older (>51 years) patients. A total of 553 patients 26–88 years of age with breast cancer metastasis diagnosis from 1 large urban practice were followed between January 1, 1999, and June 30, 2008. Comorbidity variables and survival were analyzed using Cox regression model. To assess comorbidity variables as a mediator of age-survival relationship, 2 approaches have been applied: (1) Baron Kenny approach and (2) alternative assessment to compute the percentage change in the hazard ratios (HRs). The median survival was 40 months, with 265 (47.9%) alive and 288 (52.1%) dead. Older patients had worse survival than younger patients (HR, 1.43; 95% confidence interval [CI], 1.11–1.84). Hypertension was related to survival (HR, 1.45; 95% CI, 1.12–1.89) when age and other covariates were controlled. The effect of age on survival was no longer significant after adjustment for hypertension (HR, 1.26; 95%, CI 0.97–1.65) or hypertension-augmented Charlson comorbidity score (HR, 1.24; 95% CI, 0.95–1.63). Hypertension-augmented Charlson comorbidity score or hypertension was a strong mediator of age-survival relationship among metastatic breast cancer patients, explaining survival disparity between younger and older patients by 44% and 40%, respectively. The study findings suggest that hypertension should be included in the comorbidity information for decision-making support programs. (Hypertension. 2012;59:205-211.)

Key Words: advanced breast cancer ■ comorbidity ■ hypertension ■ mediation

Breast cancer is the most common cancer among women in the United States and in other industrialized countries and is the second leading cause of death for women with cancer.1 Distant metastatic breast cancer is the most advanced stage of breast cancer and is found among 7% of women diagnosed with initial breast cancer.2 Despite the improved adjuvant treatment approaches for early breast cancer, 20–80% of these patients, depending on the initial stage and the treatment strategy followed, will develop distant metastasis within 5 years of their initial diagnosis.3

Incidence rates of breast cancer increase with advancing age, predominantly among women over 50 years of age.4,5 Mortality from breast cancer also increases with age.4,6–12 Large numbers of older women with breast cancer have coexistent diseases (comorbidities) at the time of diagnosis, which may influence their treatment options and survival.9,11,13–16

Comorbidity at diagnosis can have an adverse impact on survival. Specifically, Braithwaite et al reported that hypertension was related to survival from breast cancer diagnosis even after adjustment of age, race, and other covariates.17 The presence of comorbid conditions and its treatment could place older patients at a greater risk of dying from breast cancer. Several studies have examined the implication of comorbidities on survival in elderly breast cancer patients over 65 or 75 years of age,9,10,18,19 but the role of comorbidity as a mediator accounting for relationship between age and survival has not been clearly documented.

Although several comorbidity measurement systems exist, the Charlson comorbidity score (CCS) has been most popularly studied and considered to be a valid and reliable method of assessing comorbidity for cancer research.20 Recent reports suggest that the CCS is not entirely adequate because it does not include certain comorbidities such as hypertension.21

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States undergo menopause at the mean age of 51.22,23 and cut-point of old/young group because women in the United years biologically and clinically in terms of the breast cancer mortality from breast cancer.9,12,13,15,17,19

This study aimed to evaluate the role of comorbidities including hypertension as a mediator of disparity in survival after metastasis between younger (≤51 years) and older (>51 years) patients. The age variable was classified using 51 as a cut-point of old/young group because women in the United States undergo menopause at the mean age of 51,22,23 and women of >51 years could be different from women of ≤51 years biologically and clinically in terms of the breast cancer influencing cancer treatment and survival.5,24 To our knowledge, no study has examined the mediation effect of comorbidity between age and survival among metastatic breast cancer patients. Furthermore, we created hypertension-augmented Charlson comorbidity score (hCCS), adding hypertension as a comorbid condition to the CCS, examined the prognostic effect on survival, and compared the magnitude to which survival disparity between younger and older group may be explained by hCCS relative to CCS or hypertension alone.

Methods

Patient Selection

The study included 553 patients with the first breast cancer metastasis at 2 urban hospitals of the University of Pittsburgh Medical Center (UPMC) and by the University of Pittsburgh Cancer Institute (UPCI) Breast Cancer Program physicians. Patients diagnosed with metastatic breast cancer were identified from daily hospital clinic lists and confirmed with medical records through clinical, radiological, or pathological exams. Inclusion criteria included female patients age 18 years or older with metastatic breast cancer diagnosed between January 1, 1999, and June 30, 2008. Of 671 patients diagnosed with metastatic breast cancer during this period, 114 patients were not included because their medical records were not available for the secondary review. In addition, 4 patients were excluded because they did not have history of clinic follow-up (ie, missing information for treatment) before the first treatment or until final time observed. This study was approved by the University of Pittsburgh Institutional Review Board.

Data Collection

The medical record abstraction protocol was developed. Retrospective review of medical records according to study protocol was used. The chart abstraction form was summarized monthly by trained registered nurses. The primary data sources for abstraction were hand-written medical records, usually completed at the monthly patient visit. Race, age, estrogen receptor and/or progesterone receptor (ER/PR) status, human epidermal growth factor receptor-2 (HER2) status, number of metastatic sites, and metastatic location were assessed using the chart abstraction form completed by the primary reviewer.

The secondary chart retrieval procedure was accomplished to evaluate marital status, socioeconomic status (including insurance, education, and residential zip code), body mass index (BMI) at study entry, menopausal status, delays in treatment for breast cancer metastasis, and comorbidities according to the protocol. All predictor variables were measured at the time of metastatic breast cancer diagnosis.

Variables with more than 30% missing data such as marital status, insurance, and median household income (linked to residential zip code matched to US 2000 census summary file 325) were not included for purposes of the analysis. Missing data imputation procedure was accomplished on education, BMI (at study entry), menopausal status, and hypertension. Missing values ranged between 5% and 20% (hypertension, 5%; menopause, 11%; education, 13%; BMI, 20%).

Predictor Variables

Socioeconomic or demographic variables included age, race, education, BMI, and menopausal status. The BMI was calculated as weight in kilograms divided by a height in meters squared and categorized into 4 groups: less than 20 kg/m² (underweight), 20–24.9 kg/m² (normal), 25–29.9 kg/m² (overweight), and 30 kg/m² or higher (obese).

Pathological factors that were selected for analysis included ER/PR status, HER2 status, number of metastatic sites, and metastatic location. Determination of ER/PR and HER2 status was based on the pathological report after the first metastatic site biopsy, if available, and the initial breast cancer site biopsy, otherwise. Metastatic locations were classified into 4 groups: brain, bone, liver, and other. Lung, adrenal gland, lymph node, soft tissue, and other visceral sites were combined in “other” group due to a small sample size or non significant effect on survival according to univariate and multivariate analysis.

Treatment delay was defined as the interval measured in days between the date of initial metastatic breast cancer diagnosis and the date of the initiation of first treatment. Treatment delay interval was categorized into 3 groups: ≤4 weeks, >4 weeks to ≤12 weeks, and >12 weeks.

Comorbidity variables included hypertension, Charlson comorbidity conditions, CCS, and hCCS. The comorbidity conditions were assessed from medical records at the time of metastasis including the previous history. Hypertension was defined as a blood pressure ≥140 mm Hg systolic pressure or ≥90 mm Hg diastolic pressure (American Heart Association),26 at least twice presented at different visits. Hypertension included controlled hypertension. The CCS, a composite of 19 comorbidity conditions, was constructed using 18 comorbidity conditions (without metastatic solid tumor) that were weighted by 1 point for 10 conditions, 2 points for 6 conditions, 3 points for 1 condition, and 6 points for 1 condition.20,27 We used Deyo’s clinical comorbidity index, which adapted the Charlson comorbidity index for research relying on International Classification of Diseases (ICD-9-CM) codes.27 hCCS was constructed by assigning the weight of 1 point to hypertension and adding to the CCS (Table 1).17 The difference between CCS and hCCS was that hCCS included hypertension by 1 point with CCS conditions.

Outcome Variable

The outcome variable was an overall survival measured in months (defined as interval between metastatic breast cancer diagnosis and death or the end of follow-up period). The study ascertained the occurrence of death in 2 ways. For in-hospital deaths, the hospital records were reviewed. For out-of-hospital deaths, the data were confirmed by means of the US social security death index. Analyses censored all followed on June 30, 2008.

Statistical Analysis

Simple imputation procedure for missing data used SPSS implementation of the Expectation Maximization algorithm of Dempster, Laird, and Rubin (1977).28 The frequency distribution of complete data of variables that were imputed was compared to the available data of corresponding variables prior to imputation using appropriate 2-sample t tests for continuous variables and χ² statistics for categorical variables. Multicollinearity was assessed by using coefficient of multiple determination (R²), tolerance, and variance-inflation factor for each predictor variable using remaining covariates as its predictors.

Wilcoxon rank sum test and χ² statistics were used to identify statistically significant differences between younger and older groups for continuous and categorical variables, respectively. Logrank test was conducted to evaluate the relationship between categorical predictor variables and survival. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of younger versus older group were
Table 1. Comorbidity Conditions Used for the Construction of CCS and hCCS at the UPMC, UPCI Breast Cancer Program

<table>
<thead>
<tr>
<th>Attribute of Comorbidity Conditions</th>
<th>Comorbidity Conditions</th>
<th>Assigned Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson comorbidity conditions20</td>
<td>Myocardial infarct</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chronic pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ulcer disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mild liver disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hemiplegia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate or severe renal disease</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Diabetes with end-organ damage</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Any tumor</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate or severe liver disease</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>AIDS</td>
<td>6</td>
</tr>
<tr>
<td>Non-Charlson comorbidity condition</td>
<td>Hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

CCS indicates Charlson comorbidity score; hCCS, hypertension-augmented Charlson comorbidity score; UPMC, University of Pittsburgh Medical Center; UPCI, University of Pittsburgh Cancer Institute.

obtained from binary logistic regression for hypertension and ordinal logistic regression (assuming proportional odds) for CCS and hCCS. The Cox proportional hazards regression model was performed for univariate and multivariate analysis for categorical predictor variables (age and comorbidity variables) and both categorical and continuous covariates to yield hazard ratios (HRs) and 95% CIs. A similar modeling approach was also applied using accelerated, failure-time model assuming a Weibull error distribution.29

To assess the comorbidity variables (hypertension, CCS, and hCCS) as a mediator of age-survival relationship, we applied 2 approaches: (1) Baron Kenny approach30–33 and (2) alternative assessment to compute the percentage change in the HRs. The formal analysis to detect a mediation effect proposed by Baron and Kenny follows from the definition of a mediator: Variable M is considered a mediator if (1) X (independent variable, ie, age in this study) significantly predicts Y (outcome of interest, ie, survival in this study), (2) X significantly predicts M (potential mediator, ie, each comorbid variable in this study), and (3) M significantly predicts Y controlling for X.30–33 These criteria are assessed by estimating the following system of equations:

\[
Y = i_0 + cX \\
M = i_0 + aX \\
Y = i_1 + c'X + bM
\]

where \(i\) is an intercept coefficient.31,32

The first step of Baron Kenny approach in this study was to test the hypothesis that older women diagnosed with metastatic breast cancer had worse survival than younger women; the second step was to assess the relationship between older women with metastatic breast cancer and each comorbid variable. The third and final step was to evaluate whether each comorbid condition was associated with poor survival after adjustment for age among women with metastatic breast cancer.

An additional approach for assessing the extent to which comorbidity variables explain the young-old group difference on survival is to compare a model that includes all covariates and age with a model that include all covariates, age, and comorbidity variables and then examine percentage change in the HRs for the age-survival relationship. The percentage change in the HRs was computed as

\[
\left[ \frac{(HR_{without comorbidity} - HR_{comorbidity})}{HR_{without comorbidity} - 1.0} \right] \times 100
\]

where HR_{comorbidity} denotes the HR for the effect of age on survival after adjustment of comorbidity.21,30,33–35 A 2-tailed probability value of <0.05 was considered significant. SAS (version 9.2) and SPSS (version 17.0) were used.

Results

Analysis included 553 patients with metastatic breast cancer diagnosed between January 1, 1999, and June 30, 2008. The median survival was 40 months (range, 1–114 months), with 288 (52.1%) women having died and 265 (47.9%) having survived. Of the 553 patients included in the analysis, the majority of patients were nonblack (93.5%), postmenopausal (74.9%), ER/PR-positive (73.1%), HER2-negative (65.5%), Charlson comorbidity condition free (79.4%), and had metastasis at only 1 site (61.5%). Half of the patients (n=283, 51.2%) had more than a high school education. Most patients (73.1%) were overweight (n=253, 45.8%) or obese (n=151, 27.3%), whereas other patients were of normal weight or underweight group (n=149, 26.9%). The median treatment delay interval was 13 days (25th percentile, 0 days, and 75th percentile, 32 days). Half of the patients (n=237, 42.9%) had hypertension, and 114 (20.6%) patients had one or more of Charlson comorbidity conditions. Bone, liver, and brain metastasis were diagnosed in 298 (53.9%), 116 (21.0%), and 34 (6.1%) patients, respectively.

The distributions of patient characteristics by age group (≤51 years versus >51 years) are displayed in Table 2. The median age was 55 years (range, 26–88 years). Among the younger group (≤51 years, n=223), 107 patients had died relative to 181 patients dead in older group (>51 years, n=330). Patients of >51 years were more likely to have less than or equal to high school education (P<0.0001) and present with postmenopausal (P<0.0001) and HER2-negative (P=0.018) status compared with patients ≤51 years of age. Hypertension (P<0.0001) and ≥1 score of hCCS (P<0.0001) were more likely to be found in the older group.

Comorbidity Variables (Hypertension, CCS, and hCCS) and Age

Multivariate logistic regression was conducted for the relationship between age and three comorbidity variables (Table 3). Patients aged >51 years were >4 times as likely as patients aged ≤51 years to have hypertension (OR, 4.66; 95% CI, 3.11–6.99). Older patients had 2.58 times the odds of 1 or more CCS relative to zero CCS, 2 or more CCS relative to zero or 1 CCS, and 3 or more CCS relative to zero, 1, or 2
Older patients were more likely to have hypertension-augmented Charlson comorbidity score (hCCS) compared with younger patients; the odds of older patients was about 4 times higher to have hCCS (1 versus 0; 2 versus 0, 1; 3 versus 0, 1, 2) than younger patients (OR, 3.94; 95% CI, 2.73–5.69).

Comorbidity Variables and Outcome of Interest

Table 4 shows results for Cox regression analysis of three comorbidity variables on survival. In multivariate analysis, hypertension was found to be a significant prognostic factor (HR, 1.45; 95% CI, 1.12–1.89). The hCCS of 1 or 2 score was associated with survival compared with the zero score of hCCS (1 versus 0: HR, 1.40; 95% CI, 1.07–1.83; 2 versus 0: HR, 1.88; 95% CI, 1.22–2.89). Each score of CCS was not significantly related to survival using the zero score of CCS as a referent group in multivariate analysis. There were no significant interaction terms between age and each comorbidity variable on survival, suggesting that the relationship between age and survival was not modified by comorbidity. Additionally, the terms for the interaction among age, HER2 and each comorbidity variable were not significant, indicating that the effect of each comorbidity variable on survival in...
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Her2-positive and in Her2-negative status was not modified by age group.

Comorbidity Variables Explaining the Age-Survival Relationship

Comparing a model that included all covariates and age on survival with a model that included all covariates and age and each of comorbidity variables on survival, introduction of hypertension, CCS, and hCCS into a model that included covariates and age, reduced the HR of age on survival by 40%, 14%, and 44%, respectively (Table 5). Furthermore, the effect of age on survival was no longer significant after adjustment of hypertension (HR, 1.26; 95% CI, 0.97–1.65) or hCCS (HR, 1.24; 95% CI, 0.95–1.63), suggesting that hypertension and hCCS strongly mediate the age-survival relationship.

In the present study, we found that hypertension/hCCS was a predictor of survival after breast cancer metastasis, and hCCS or hypertension was better than CCS alone (14%) to explain disparity between the younger and older group in survival by 44% and 40%, respectively, after accounting for all covariates. Moreover, hypertension and hCCS were found to be strong mediators because the effect of age on survival was not significant after adjustment of hypertension or hCCS.

Consistently with previous studies, our study found that older age had an adverse impact on survival than younger group (HR, 1.43; 95% CI, 1.11–1.84; Table 5). Specifically, Largillier et al reported that excess mortality rate increased with patients >50 years of age relative to patients <50 years in stage IV breast cancer. Several studies showed that younger patients had better survival than older patients, and this difference in survival between age groups does not seem to be the result of the difference of treatment but suggests the influence of age-related factors such as comorbidity conditions that place the older group at greater risk of poor prognosis on the course of metastatic disease.

In agreement with previous studies, this study demonstrated that comorbidity conditions increased with age (hypertension: OR, 4.66; 95% CI, 3.11–6.99; CCS: OR, 2.59; 95% CI, 1.58–4.24; hCCS: OR, 3.94; 95% CI, 2.73–5.69). Hypertension was the most prevalent comorbidity condition among breast cancer patients and was more likely to be found in older patient group. Hypertension can
potentially be an important risk factor for cancer morbidity and mortality. Cell death by apoptosis can influence the growth of vascular smooth muscle cells and relevant significant anomalies have been observed in hypertension. Increased proliferation of vascular smooth muscle cells responds exaggeratedly to growth stimuli, which is characterized by shortening of the cell cycle. This mechanism may lead to increased cellular proliferation. Moreover, Dy et al identified the aberrations of carcinogen binding to exoribonucleic acid in lymphocytes of hypertensive subjects. We observed an association between hypertension and survival after diagnosis of metastatic breast cancer even after adjustments of age and other covariates (Table 4), corroborating previous literature.

Our chart abstraction procedure detected Charlson comorbidity in 21% of cases, which is in concordance with other published studies. In the present study, we found that CCS for 1-unit increase had a marginal adverse effect on survival in univariate analysis (data not shown) but was not significant after accounting for age and other covariates in consistent with another study. Additionally, CCS by itself was not a strong mediator of age-survival relationship; however, hCCS or hypertension explained the survival disparity between younger and older age group by 44%, 40% relatively, compared with 14% of CCS alone, indicating that hCCS or hypertension was a better than CCS to describe the age-survival relationship.

The standard Charlson list of comorbidities excludes hypertension. Based on the study results, we recommend that future studies of clinical predictors of survival after breast cancer metastasis should not rely only on Charlson comorbidities but also include, at minimum, hypertension.

This study had limitations. We were unable to evaluate the confounding effect of antihypertensive treatment on the relationship between hypertension and survival. Blood pressure medications such as calcium channel blockers and diuretics not only regulate blood pressure but also have a mitogenic effect. In addition, we did not consider cardiometabolic factors such as low-density lipoprotein cholesterol or glycohemoglobin (hemoglobin A1c), which were unavailable for study analysis of their impact on survival.

This study did not include 114 patients because medical records were unavailable for the secondary review, which could induce the possible sources of selection bias. Furthermore, our study collected data from one large urban practice, making the results less generalizable than studies conducted on multiple sites.

We performed sensitivity test using available data of variables before the imputation procedure compared with complete data of corresponding variables that were imputed, and there was no apparent difference in the frequency distribution and in the univariate analysis. In addition, the mediation effect was measured as a percent change of hazard rate in Cox proportional hazards model. We were not able to conduct the direct significant test of mediation hypothesis because survival analysis was not feasible in structural equation modeling software packages (eg, AMOS, Mplus). Our study findings, however, were fairly robust since similar results were obtained using semiparametric, Cox regression and parametric, accelerated failure-time models (data not shown).

**Perspectives**

With the use of a large database reflective of current metastatic breast cancer treatment, this study used a uniform protocol for data collection and examined prognostic factors in a comprehensive fashion. Findings of this study suggest that hypertension should be included in the comorbidity information for decision making support programs to aid in the consultation for patient care, and efforts that aim to manage comorbid illness in older women may reduce the survival disparity between older and younger women.

**Disclosures**

None.

**References**

Comorbidity as a Mediator

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