MORTALITY AFTER METASTATIC BREAST CANCER: CO-MORBIDITY AS A MEDIATOR OF AGE ON SURVIVAL, AND DELAYS IN TREATMENT FOR BREAST CANCER METASTASIS

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Submitted to the Graduate Faculty of

Department of Epidemiology

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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Patients with breast cancer metastases have very poor survival. Delays in the initiation of breast cancer treatment may adversely affect survival. Comorbid illness is more common in older women. Comorbid illness may explain effects of age on metastatic breast cancer survival outcomes. Comorbid illness may affect treatment delay.

The purpose of the present study was to 1) identify factors related to survival following metastatic breast cancer diagnosis, 2) assess the impact of delay in treatment on survival while controlling for immortal time bias, and 3) evaluate the role of comorbidity as a mediator of survival disparity between younger (≤ 51 years) and older (> 51 years) patients.

A total of 557 patients with the initial breast cancer metastasis diagnosis have been followed up between January 1, 1999 and June 30, 2008. Prognostic factors and outcomes of these patients were analyzed using log-rank test and Cox regression model, demonstrating that hypertension, ER/PR, HER2 status, number of metastatic sites, and BMI at metastatic breast cancer diagnosis were the most relevant prognostic factors for survival. Backward stepwise selection of covariates was conducted among 553 patients and showed that treatment delays of > 12 weeks had a marginal impact on poor survival

(HR 1.76, 95% CI 0.99-3.13). Moreover, the interval of 12-24 weeks, compared to the interval of 4-12 week was a prognostic factor for survival from first treatment (HR 2.39, 95% CI 1.19-4.77). To assess comorbidity variable as a mediator of age-survival relationship among 553 patients, we applied two approaches: 1) Baron Kenny approach, and 2) alternative assessment to compute the percentage change in the HRs. Hypertension was related to survival (HR 1.45, 95% CI 1.12-1.89) and hypertension augmented Charlson comorbidity score (hCCS) explained survival disparity between young and old patients by 44% compared to 40 % of hypertension and 14% of the Charlson comorbidity score (CCS).

Looking for opportunities to improve public health, the present study identifies modifiable factors associated with variable outcomes after diagnosis of metastatic breast cancer.

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ACKNOWLEDGEMENT

I would like to take this opportunity to acknowledge everybody who supported and guided me through graduate school, individuals who contributed to this study, and those who helped me to become a cancer epidemiologist. I have been extremely fortunate to be surrounded by people who supported my education and who gave me the opportunity to perform this research.

First and foremost, I would like to express my deepest gratitude to Dr. Joel Weissfeld. As my advisor and mentor throughout the research, he has been an invaluable resource. His scholarly insights, questions, and critiques made successful completion of this dissertation possible. I cannot thank him enough for his endless support, encouragement, and generosity of time committed to this effort. Without his unflinching help, this work would not have been completed. He is indeed a model of scientific excellence and an enthusiastic epidemiologist that I always admire.

The members of my committee have been an indispensable resource throughout the research. This study would not have been feasible without their dedication and invaluable help. Dr. Margaret Rosenzweig has been a dedicated advisor and wisdom mentor, always willing to share her knowledge and wisdom. Without the support of Dr. Margaret Rosenzweig, a principal investigator of the Metastatic Breast Cancer Study, this work would not have been possible. Dr. Susan M. Sereika served an invaluable statistical

consultant, devoting considerable time to this study. Dr Faina Linkov provided critical insights to this study, as well as an abundance of thoughtful comments and editing support; her excellence work as a scientific mentor, and her words of encouragement are very much appreciated.

I would like to thank Sondra Swain and Patricia M. Gordon for their dedication of medical record abstraction and collaboration on this research. I am sincerely grateful for their friendship and support. I would also like to thank Kaitlyn Ragula, a medical record manager for her meticulous work of numerous charts arrangement. Special thanks to Colleen Shaughnessy, Kerry Ryan, Cynthia Hinshaw, and Lara Burke for their outstanding work of chart abstraction. Many thanks to Jacqueline Simon and Kathleen Slavish for their countless and unwavering support. I am proud to call them my friends and colleagues. I dedicate this work to participants who volunteered in the hope of fostering the metastatic breast cancer study. I thank those with whom I worked at the Epidemiology Data Center, along with my other friends and colleagues at the University of Pittsburgh.

Finally, I must acknowledge the love and support of my family in Korea, who never doubted my path. I would not be where I am today without their love and endless prayers. Thank you, Mom and Dad, your endless encouragement and unshakable faith in my achievement were critical to my success. I dedicate this work to you. I thank you, my younger brother-Jae Hun, and his wife-Hyang Suk for their patience, dedication, and support through all these years.

Last, but utmost, I thank God Almighty for providing me with the opportunity and ability to complete this work.

1.0 INTRODUCTION

Breast cancer is the most commonly diagnosed solid tumor among women in the US and in most other industrialized countries, and the second leading cause of death for women with cancer.[1] Distant metastatic breast cancer is the most advanced stage of breast cancer and occurs in less than 10% of breast cancer patients, estimated 90,000 new cases per year, and has different prognosis.[2-5] The 5-year relative survival for women diagnosed with meatstatic breast cancer between 1999 and 2006 was 23%.[6]

Despite the improved treatment approaches for the metastatic breast cancer, survival time for patients with metastasis varies greatly, ranged from less than 9 months to over 3 years of median survival duration.[7] Patients diagnosed with metastatic breast cancer can be considered a heterogeneous population whose clinical outcomes vary depending on a variety of host factors.[8] Several prognostic factors influencing survival outcomes were reported by the recent consensus paper on medical treatment of metastatic breast cancer. These factors include pathological factors such as hormone receptor (estrogen receptor (ER) and/or progesterone receptor (PR)) status, human epidermal growth factor receptor-2 (HER2/*neu*) status, and the location and extent of metastases (visceral versus non-visceral).[9] Other investigators have demonstrated adverse survival outcome after diagnosis with metastatic breast cancer in relation to demographic factors including being of older age, black race, low socio-economic status (SES), and higher

body mass index (BMI).[10-23] Other factors which have been associated with worse survival include clinical factors such as hypertension and co-morbid illness.[24-30]

Finally, treatment-related factor such as delayed treatment interval has been increasingly focused for evaluating its association with survival following metastatic breast cancer diagnosis. In previous studies, treatment delay has been defined as the time between the date of diagnosis of metastatic breast cancer and the date of the initiation of the first course of treatment. Several studies have shown that one to three month delay in the start of treatment had a reduced likelihood of survival[31-33], while others did not support the hypothesis that treatment delay may adversely affect survival.[34-42]

These inconsistent results may be attributed to differences in the selection of study populations, difference in measurement of survival lengths, and availability of covariates.[43] Although multiple studies examining prognostic factors individually may be helpful in predicting survival among patients with metastatic breast cancer, more comprehensive information concerning prognosis is needed.

Incidence and mortality rates for breast cancer increase with advancing age, and this increase has occurred predominantly in women over 50 years, who are considered menopausal.[8, 12, 44-50] The higher prevalence of comorbidity could explain the poor survival outcomes among older patients[47, 48, 51-54], but the role of comorbidity as a mediator which may explain the survival difference between younger and older patients has not been clearly documented.

Furthermore, hypertension is the most prevalent comorbidity among older breast cancer patients, and it affects mortality from breast cancer.[28, 47, 50, 53, 55, 56] Hypertension can potentially be an important risk factor for cancer mortality. For example, cell death

by apoptosis can influence the growth of vascular smooth muscle cells (VSMCs) and the increased proliferation of VSMCs responds exaggeratedly to growth stimuli, which is characterized by shortening of the cell cycle. This mechanism may lead to increased cellular proliferation.[57] Charlson comorbidity index (CCI), which has been widely employed and considered to be a valid and reliable method of assessing comorbidity for cancer research[58], did not include certain comorbidities such as hypertension that did not contribute to a high relative risk in their study population.[48, 59]

This study aimed to 1) identify factors related to survival after diagnosis of metastatic breast cancer, 2) evaluate the effect of delays in the initiation of treatment on survival among metastatic breast cancer patients, and 3) assess the role of comorbidity, including hypertension, as a mediator of explaining the difference in survival following metastasis between younger and older patients.

2.0 SPECIFIC AIMS AND HYPOTHESES

In this study, the following specific aims and hypotheses are addressed to identify predictor variables influencing survival following diagnosis of metastatic breast cancer.

1) **Specific aim 1: To assess factors associated with mortality after breast cancer metastasis.**
    a. Aim 1.1: To examine the relationship between demographic or socioeconomic factors and survival following metastatic breast cancer diagnosis. *We hypothesize that older age, black race, less than or equal to high school education, low income level, higher BMI, and post menopausal status are associated with poorer survival in women with metastatic breast cancer.*
    b. Aim 1.2: To investigate the association of pathological factors with survival. *We hypothesize that being ER or PR negative, HER2 negative, increasing number of metastatic organs, and brain, bone, and liver metastasis are related to adverse survival outcomes.*
    c. Aim 1.3: To explore whether clinical factors are related to survival. *We hypothesize that hypertension, Charlson comorbidity conditions, and*

Charlson comorbidity score negatively impact survival among women metastatic breast cancer.

2) **Specific aim 2: To evaluate the effect of delays in treatment for breast cancer metastasis on survival.** *We hypothesized that delayed treatment is associated with decreased survival among women with metastatic breast cancer.*
3) **Specific aim 3: To examine comorbidity as a potential mediator of survival disparity between younger and older women diagnosed with metastatic breast cancer.**
    a. Aim 3.1: To assess the relationship between age and survival among women with metastatic breast cancer. *We hypothesize that older women have poorer survival following metastatic breast caner diagnosis than younger women.*
    b. Aim 3.2: To evaluate the association between age and comorbidity among women diagnosed with metastatic breast cancer. *We hypothesize that higher prevalence of comorbidity is found in older women than younger women.*
    c. Aim 3.3: To examine whether comorbidity influences survival after metastatic breast cancer diagnosis. *We hypothesize that comorbidity has adverse impact on survival following metastatic breast cancer diagnosis.*
    d. Aim 3.4: To measure the extent to which comorbidity mediates the association between age and survival after metastatic breast cancer diagnosis. *We hypothesize that control for comorbidity attenuates the*

association between age and poor survival following metastatic breast cancer diagnosis.

3.0 LITERATURE REVIEW

3.1 EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is the most commonly diagnosed tumor among women in the US and in most other industrialized countries, and the second leading cause of death for women with cancer. [1] Incidence of breast cancer from 2000 to 2004 in the US was 125.3 per 100,000 and after a 6% decrease from 2002 and 2003, the incidence rates from 2003 to 2006 remains unchanged.[1, 60] The new cases of invasive breast cancer were found in the estimated 209,060 cases in 2010.[60] Breast cancer mortality rate was 25.5/100,000 between 2002 and 2004, and 40,230 deaths occurred in 2010 in the US.[60]

Distant metastatic breast cancer is the most advanced stage of the disease, which carries poor diagnosis (Table 1). Metastatic breast cancer occurs in less than 10% of breast cancer patients, estimated 90,000 new cases per year, and has different prognosis based on extent of metastases. [2-5] Although great improvements have been made in the adjuvant treatment of early breast cancer, 20% of patients initially diagnosed with node-negative early stage breast cancer (N0), and at least 50-60% of patients with positive nodes at diagnosis develop metastatic breast cancer. [61-64]

The medical treatment of metastatic breast cancer offers a wide range of options including chemotherapy, hormonal therapy, therapy with antibodies against growth

factors relevant to the disease, vaccine therapy, immunologic therapy, and other supportive measures.[9] Even though patients with metastatic breast cancer are treated uniformly with standard therapy, the treatment of metastatic breast cancer remains palliative. The survival for patients diagnosed with metastasis may range from a few months to several years.[7] Patients with metastatic breast cancer represent a heterogeneous group whose prognosis and clinical course may depend on a wide variety of host factors.[8] Improved evaluation of the profile of prognostic factors can not be overemphasized in women with metastatic breast cancer.

Table 1. Stage distribution and 5-year relative survival by stage at diagnosis for 1999-2006, all races, females (National Cancer Institute Surveillance, Epidemiology, and End Results Programs (SEER)

Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 1999-2006, All Races, Females

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized (confined to primary site)	60	98.0
Regional (spread to regional lymph nodes)	33	83.6
Distant (cancer has metastasized)	5	23.4

A recent consensus paper on medical treatment of metastatic breast cancer reported a number of prognostic factors influencing survival (Table 2). These factors included hormone receptor status such as estrogen receptor (ER) and/or progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2/*neu*) status, the location and extent of metastases (visceral versus non-visceral), performance status, disease-free interval, prior adjuvant therapy, and prior therapy for metastatic breast cancer.[9]

Table 2. Prognostic factors in patients with metastatic breast cancer

Prognostic factor	Favorable	Unfavorable
Performance status	Good	Poor
Sites of disease	Bone, soft tissue	Viscera, CNS
No. of sites of disease	Few	Multiple
Hormone receptor status	Positive	Negative
Her-2/*neu* status	Negative	Positive (significance less clear in Her-2/*neu* inhibitors era)
Disease-free interval	> 2 years	< 2 years
Prior adjuvant therapy	No	Yes
Prior therapy for MBC	No	Yes

CNS, central nervous system; MBC, metastatic breast cancer.

3.2 PROGNOSTIC FACTORS FOR BREAST CANCER SURVIVAL

3.2.1 Demographic or socio-economic factors

3.2.1.1 Age

Breast cancer incidence rates increases with advancing age, and breast cancer is a disease primarily seen in older women (Table 3).[65] The age-incidence rate changes around the menopausal period, most likely due to hormonal change ten years earlier, levels off at the 40-50 years of age (Clemmesen's hook), and then increases again to a peak at 75 years, and declines.[44, 65] Incidence rate for female breast cancer rises over time, and this increase has been occurred predominantly in women over the age of 50.[44, 65]

Older age has negative impact on survival after breast cancer diagnosis.[10-12] Specifically, Cluze et al. reported that excess mortality rate increased with age in stage IV

breast cancer.[12] It is generally accepted that young age at diagnosis is associated with more aggressive breast cancer and relatively poor survival [66], but several studies showed that pre menopausal patients had better survival than post menopausal patients.[8, 67] Data from the Surveillance, Epidemiology, and End Results Program (SEER) showed that breast cancer mortality declined significantly from 7.0/100,000 in 1973 to 6.2/100,000 in 1988 in women younger than 50 years. On the contrary, mortality rate in older women increased from 88.4/100,000 in 1973 to 93.0/100,000 in 1988, an increase of 5.2%.[44] Largiller et al. reported that women over the age of 50 had significantly lower survival rates, indicating that post menopausal patients have higher risk of mortality than pre menopausal patients.[8] Postmenopausal patients have been found to have lower response rate to chemotherapy. The increase in side-effects of chemotherapy inducing dose reduction, and loss of efficiency in older women, as well as more comordid conditions may explain this result.[7, 8]

Table 3. Percent of U.S. women who develop breast cancer over 10-, 20-, and 30-year intervals according to their current age, 2005-2007

Percent of U.S. Women Who Develop Breast Cancer over 10-, 20-, and 30-Year Intervals According to Their Current Age, 2005–2007†			
Current Age	**10 Years**	**20 Years**	**30 Years**
30	0.43	1.86	4.13
40	1.45	3.75	6.87
50	2.38	5.60	8.66
60	3.45	6.71	8.65

†Source: Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds). *SEER Cancer Statistics Review, 1975–2007*, National Cancer Institute. Bethesda, MD, based on November 2009 SEER data submission, posted to the SEER Web site, 2010.

3.2.1.2 Ethnicity

Increasing evidence suggests that breast cancer in black women demonstrates unique clinical behavior compared to white women. Nationally, black women have an overall lower incidence of breast cancer than do white women, but black women are more likely to die of invasive breast cancer (34.5 vs. 25.4 death per 100,000 women).[68] Despite modest overall improvements in breast cancer survival rates over the last two decades, the rates for black women have not improved, and the gap in life expectancy between white and black women diagnosed with breast cancer continues to widen. From 1975 to 2002, Surveillance, Epidemiology, & End Result (SEER) data indicate that white women had a 29% increase in breast cancer incidence and a 22% decrease in morality while black women experienced an identical 29% increase in breast cancer incidence and, 16% increase in mortality during the same time period (Figure 1).[69]

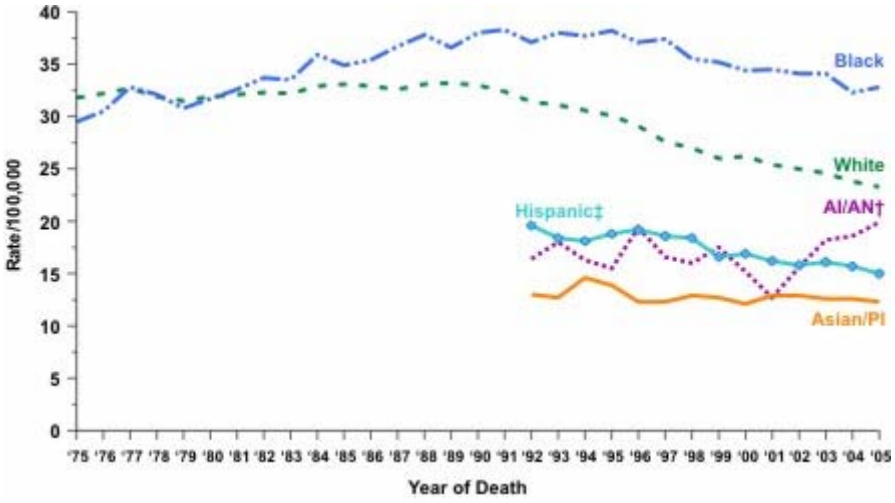

Figure 1. Breast cancer mortality by race (based on SEER data)

The 5-year survival for women diagnosed with meatstatic breast cancer between 1996 and 2002 was 28% for whites and only 16% for blacks. Of particular concern is that

this survival disparity is growing compared with the 1975 to 1979 period, when the 5-year cancer-specific survival was 18% for whites and 15% for blacks.[70] Understanding this stage-specific survival disparity is challenging and has been rarely explored in previous studies.

3.2.1.3 Obesity

Previous studies have reported that overweight or obesity, estimated by body mass index (BMI) is associated with increased risk of breast cancer morbidity and adverse survival outcomes in pre and postmenopausal women with breast cancer.[22, 23] Several mechanisms could explain these observations: high concentrations of estrogen, estradiol, and testosterone in overweight and obese women with breast cancer; lower level of sex hormone-binding globulin, resulting in higher levels of free estradiol and free testosterone. Estrogen-sensitive tissue in overweight and obese women may be subject to higher estrogen stimulation, inducing more rapid growth of malignant cells.[19]

Weight gain post-diagnosis of breast cancer is common and is likely due to increases in fat-free mass. However, weight gain in the immediate period after breast cancer diagnosis has not adverse impact on prognosis, indicating that overweight or obesity over the lifespan has greater magnitude of impact on survival since breast cancer diagnosis.[20]

On the other hand, the weight loss of over 10% after breast cancer diagnosis increased the risk of breast cancer mortality compared to being weight stable [11, 71], and this risk was more pronounced among women who were obese (BMI $\geq$ 30kg/m^2) before diagnosis.[20]

3.2.1.4 Socio-economic status (SES)

Women with low SES tend to have lower risk of developing breast cancer, but at higher risk of mortality. Differences in reproductive behavior may account for the social difference in breast cancer incidence; women of higher SES, in general, have lower parity, older age of first birth, greater frequency of childlessness, a shorter duration of breast-feeding, and a later age at menopause, which are all known to increase risk of breast cancer.[15] The etiology of social differences in breast cancer mortality is less known, and previous studies did not achieve a consensus on the relationship between the SES and breast cancer survival, which may be explained by differences in measurement of SES factors. For example, Dalton et al showed that decreasing disposable income with less education were reported to be a risk factor for being diagnosed with a high-risk breast cancer [16], and family income was only related to survival among SES factors in study conducted by Rezaianzadeh et al.[17] Low SES based on women's occupation was shown to be a strong prognostic factor [18], but the study to evaluate the effect of the SES including occupation as well as education on survival in breast cancer patients found no significant association.[72]

3.2.2 Pathological factors

3.2.2.1 HER2 status and ER or PR status

Previous studies have pointed out differences in survival outcomes among patients with breast cancer associated with tumor-related factors such as hormone-receptor status and tumor histology. Basal like tumors ("triple negative") which exhibit low expression of

human epidermal growth factor receptor-2 (HER 2) and estrogen (ER), show less favorable patient outcomes than ER positive tumors. [73, 74]

Additionally, several studies reported that ER or PR-negative status is related to poor response to treatment or worse survival outcomes following metastatic breast cancer diagnosis.[7, 8, 64, 75-81] Highest mortality rate in ER-positive tumors occurred later than in ER-negative tumors. Grasic et al. reported that the difference of breast cancer mortality between ER-negative and ER-positive occurred from 5 year on, and the hazard in ER-positive was higher than ER-negative.[82] Adjuvant hormonal treatment with tamoxifen diminishes the risk for death in ER-positive tumors, and the relative gain of mortality in tamoxifen treated compared to non-treated group increased at 5 years.[83]

3.2.2.2 Metastatic location and number of metastatic organ sites

Prognosis varies according to patterns of metastasis.[2] Breast cancer typically spreads hematogenously, producing lung and bone metastasis. Bone is the most frequent site of metastasis with the occurrence in 40-55% of metastatic patients in previous studies.[8, 76] Women with a single metastasis to cortical bone may live for many years, whereas women with metastasis to vital organs (e.g., lungs, liver, bone marrow, brain, heart) face a poorer prognosis.[61]

Metastatic breast cancer has worse survival outcomes compared to typical breast cancer carcinoma, which may be attributed to increasing number of organ sites affected by metastasis. Previous work validated that increasing number of metastatic organ sites at diagnosis was a major prognostic factor for survival.[10, 11, 64, 79, 84]

Considering those issues, the inclusion of metastatic location and number of metastatic organ sties at diagnosis as covariates in the study analysis is necessary to

evaluate prognostic factors related to survival after diagnosis of metastasis, limiting the possible confounding effect on study result.

3.2.3 Clinical factors

3.2.3.1 Treatment delay

Treatment-related factor such as delays in receiving treatment after diagnosis of breast cancer has been increasingly investigated as a reason for the poor survival in women diagnosed with breast cancer. Treatment delay has been measured as the time from the date of diagnosis of breast cancer to the date of the initiation of the first treatment. It is generally assumed that the greater the delay in receiving treatment for breast cancer the worse the prognosis outcomes.

Previous studies demonstrated that one to three month delay in the start of the treatment has a reduced likelihood of survival. [31-33] Rechards et al conducted a meta analysis for evaluating the association of delayed treatment interval with survival outcomes, and concluded that patients with a delay of three to six months from the symptom recognition to the start of treatment had lower survival rate than patients with a delay of less than three months, and that a delay of more than six months was related to poorer survival than was a delay of less than six months.[85]

However, there is disagreement regarding whether survival after diagnosis of breast cancer is related to the lengths of the delay in the initiation of treatment (Table 4). Several studies observed that the longer delays was related to lower survival [31, 43, 86-91]; other studies did not support the hypothesis that delays in treatment after breast cancer diagnosis may adversely influence survival.[34-42] These conflicting results may be

explained by differences in the selection of patients, by difference in the cut-offs used to categorize delay interval, by difference in measurement of survival lengths and by availability of clinical, socio-economical and biological covariates.[43]

In addition, factors influencing delays in receiving treatment include age, ethnicity, socio-economic status including education, income level, and psychosocial factors such as anxiety, misconceptions about cancer, and cultural differences.[34, 35, 41-43, 89, 92, 93] Delay period was shorter among older compared to younger women diagnosed with breast cancer, assuming that the diagnostic work-up is more difficult in younger women due to a higher frequency of dense and lumpy breast tissues in this age-group.[89] Further studies regarding factors influencing delays in initiation of treatment are needed.

Table 4. Summary of previous work for the effect of treatment delay on survival

Previous Study		Study design and study population	Delay interval
Studies supporting hypothesis			
Gorin et al	(2007)	Retrospective, Medicare enrollees	≤ 3 months vs. > 3 months
Gorin et al	(2006)	Retrospective, Medicare enrollees	≤ 1 month vs. > 1 month
Kievit et al	(2002)	Literature review	Per month
Richards et al	(1999)	Retrospective, the breast unit at Guy's hospital	< 12 weeks vs. 12-26 weeks
Hermann et al	(1985)	Prospective, Cleveland clinic	≤ 2 months vs. 2-<6 months vs. ≥ 6 months
Sheridan et al	(1971)	Retrospective, St Vincent hospital tumor clinic	1-3 month vs. 3<-6 months
Studies not supporting hypothesis			
Elmore et al	(2005)	Retrospective, Yale-New Haven hospital	≤ 1 month vs. > 1 month
Hershman et al	(2005)	Retrospective, Henry Ford Health System tumor registry	≤ 1 week vs. 1-2 weeks vs. > 2 weeks
Machiavelli et al	(1989)	Retrospective, institutions of GOCS Hospital Privado Guemes and Hospital Privado de Comunidad	< 3 months vs. 3-6 months vs. > 6 months
Charlson et al	(1985)	Retrospective, Yale-New Haven hospital	< 3 months vs. 3-6 months vs. > 6 months
Dennis et al	(1975)	Retrospective, State University Hospital-King County hospital center	< 1 month vs. 1 month vs. > 1 month

3.2.3.2 Comorbidity

Cmorbidity, defined as the coexistence of various chronic illnesses in addition to the index disease (i.e., breast cancer), is an increasing problem due to its adverse effect on

the prognosis in breast cancer patients.[55] Breast cancer patients with comorbidity are likely to have a lower survival compared to patients without comorbidity, regardless of other prognostic factors such as age, and breast cancer stage at diagnosis.[24-30, 53] Satarioano et al reported that comorbidity is a major prognostic factor in patients diagnosed with breast cancer.[94]

The adverse impact of comorbidity on survival may be due to the physical burden of chronic illnesses and its interaction with the cancer and its treatment. Comorbidity conditions can increase the toxicity of specific treatments for cancer, and substantially reduce remaining life expectancy by canceling gains with therapy. Thus, patients with severe medical comorbid diseases do not receive appropriate therapy for breast cancer, which may lead to lower survival.[95]

Previous studies found that prevalence of comorbid conditions increased with age.[47, 48, 56, 96] Four out of five patients aged 65 years or older have one or more comorbid conditions.[56] The presence of comorbidity and its treatment for their control could place older patients at greater risk of adverse impact on certain treatment (e.g., chemotherapy, or surgery), resulting in detrimental prognosis after breast cancer diagnosis.[56] Yancik et al demonstrated that women older than 75 years diagnosed with breast cancer were more likely to die from comorbid diseases than from other prognostic factors.[97]

Hypertension is the most prevalent comorbid disease among older breast cancer patients, and its presence is related to negative outcomes from breast cancer.[28, 47, 50, 53, 55, 56] Several studies suggest a link between hypertension and risk of breast caner morbidity and mortality. For example, cell death by apoptosis can influence the growth of vascular smooth muscle cells (VSMCs) and the increased proliferation of VSMCs responds

exaggeratedly to growth stimuli, which is characterized by shortening of the cell cycle. This mechanism may lead to increased cellular proliferation.[57] Studies of the relationship between antihypertensive drugs and risk of cancer demonstrated significant association between antihypertensive drugs such as diuretics or calcium channel blockers and breast cancer risk [98] [99], but biologic explanation for these association has not been elucidated.

4.0 FACTORS ASSOCIATED WITH MORTALITY AFTER BREAST CANCER METASTASIS

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4.1 ABSTRACT

Background: It is generally accepted that patients with breast cancer metastases have very poor survival. Metastatic breast cancer patients can be considered a heterogeneous population with a varied clinical course, which underscores the need for accurate prediction of survival based on prognostic factors. The purpose of the present study was to identify factors related to survival in breast cancer patients after diagnosis with metastatic disease.

Populations and Methods: A total of 557 patients with the first breast cancer metastasis diagnosis seen at one large urban practice have been retrospectively followed up between January 1, 1999 and June 30, 2008. Demographic, tumor characteristics, clinical factors, and outcomes of these patients were analyzed by using log-rank test and Cox regression model.

Results: The median survival length was 40 months (range 1-114 months) with 269 (48.3%) alive and 288 (51.7%) dead. This study demonstrated that a history of hypertension, ER/PR status, HER2 status, number of metastatic sites, and BMI at diagnosis with metastatic breast cancer were the most relevant prognostic factors for survival after metastasis.

Conclusion: The present study findings may form a foundation for the growing corpus of knowledge explaining the outcome differences in treatment of patients with metastatic breast cancer, potentially helping to create more personalized treatment approaches for this vulnerable group.

Key words: advanced breast cancer, prognostic factors, comorbidity

4.2 INTRODUCTION

Breast cancer is the most common cancer in women in the United States and in other industrialized countries, and the second leading cause of death for women with cancer.[100] Despite improved techniques for breast cancer screening, as many as 7% of women present with metastatic disease at the time of diagnosis.[101] While most women are diagnosed at an early stage, 20% to 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.[102]

Treatment of metastatic breast cancer remains palliative despite recent advances in the treatment of this disease. Survival time for patients with metastasis varies greatly; median survival duration may range from less than 9 months to over 3 years.[7] Patients with metastatic breast cancer represent a heterogeneous group whose prognosis and clinical course may depend on a wide variety of host factors.[8] These observations emphasize the importance of defining prognostic factors in women with metastatic breast cancer.

A recent consensus paper on medical treatment of metastatic breast cancer reported several factors influencing clinical outcomes. These factors included hormone receptor, human epidermal growth factor receptor-2 (HER2/*neu*) status, the location and extent of metastases (visceral versus non-visceral), performance status, disease-free interval, prior adjuvant therapy, and prior therapy for metastatic breast cancer.[9] Other investigators observed poor survival after diagnosis with metastatic breast cancer in relation to older age, black-race, low socio-economic status (SES), and higher body mass index (BMI).[10-23] Other important factors which have been correlated with worse survival

include a history of hypertension and co-morbidities.[24-30] Interestingly, not every study identifies the same set of risk factors explaining variation in prognosis following breast cancer metastasis. Although multiple studies examining factors individually may be helpful in predicting survival among patients with metastatic breast cancer, more comprehensive information concerning prognosis are needed.

This study aimed to identify factors related to survival in patients with metastatic breast cancer. The study used data from 557 patients with metastatic breast cancer seen at one large urban practice between January 1, 1999 and June 30, 2008.

4.3 POPULATIONS AND METHODS

4.3.1 Patients Selection

The study included 557 patients with the first breast cancer metastasis seen at two urban hospitals (Montefiore and Magee) of the University of Pittsburgh Medical Center (UPMC) and by the University of Pittsburgh Cancer Institute (UPCI) Breast Cancer Program physicians. Patients with metastatic breast cancer were identified from daily hospital clinic lists and confirmed with medical records through clinical, radiological, or pathologic exams. Inclusion criteria included female patients aged eighteen 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 excluded because their medical records were unavailable for the secondary review. This study was approved by the University of Pittsburgh Institutional Review Board.

4.3.2 Data Collection

The medical record abstraction protocol was developed. See Figure 2. Retrospective review of medical records according to study protocol was utilized. Chart abstraction form was summarized monthly by trained registered nurse. The primary data sources for abstraction were hand written medical records, usually completed at the monthly patient visit.

Age, race, estrogen receptor (ER) and/or progesterone receptor (PR) status, HER2 status, number of metastatic sites and metastatic location were assessed using the chart abstraction form completed by primary reviewer. Quality guaranteed protocol for the secondary chart review was established. The weighted kappa coefficients of secondary chart abstraction with n = 23, and of repeated chart abstraction with n = 23 for Charlson comorbidity score were 0.88 (95% CI 0.64-1.00) and 0.88 (95% CI 0.66-1.00), respectively; secondary and repeated chart abstraction for hypertension were 0.93 (95% CI 0.79-1.00) and 1.00 (95% CI 1.00-1.00), respectively.

The secondary chart retrieval procedure was performed to evaluate marital status, socioeconomic status (SES) including insurance, education, residential zip code, BMI at breast cancer diagnosis and at study entry, weight change (difference weight between at metastasis and weight at breast cancer diagnosis), menopausal status, and comorbidities according to the protocol. All independent variables were measured at the time of metastatic breast cancer.

Variables with more than 40% missing data such as marital status, insurance, BMI at breast cancer diagnosis and weight change were excluded for purposes of the analysis. Missing data imputation procedure was accomplished on education, median household income, BMI (at study entry), menopausal status and hypertension having missing values ranged 5% to 35% (hypertension 5%, menopause 11%, education 13%, BMI 20%, income 35%).

4.3.3 Independent variables

Demographic or socioeconomic variables included age, race, education, median household income, BMI, and menopausal status. The median household income was linked to residential zip code matched to U.S. 2000 census summary file 3.[103] The BMI was calculated as a weight in kilogram (kg) divided by a height in meters squared and classified into four groups: less than 20kg/m^2 (underweight), 20-24.9kg/m^2 (normal), 25-29.9kg/m^2 (overweight), 30kg/m^2 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 used the pathologic report following the first metastatic site biopsy, if available, and the initial breast cancer site biopsy, otherwise. Metastatic locations were categorized into four 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.

Clinical variables included a history of hypertension, Charlson comorbidity conditions and Charlson comorbidity score. Hypertension was defined as a blood pressure greater than or equal to 140 mmHg systolic pressure or greater than or equal to 90 mmHg diastolic pressure (American Heart Association) [104], at least twice presented at different visits. Hypertension included controlled hypertensives. The Charlson comorbidity score, a composite of 19 comorbidity conditions was constructed using 18 comorbidity conditions (without metastatic solid tumor) which were weighted by 1,2,3, or 6. The sum of the weighted comorbidity conditions has a theoretical range between 0 and 31. Final Charlson comorbidity score was obtained by adding the age-comorbidity combined risk score.[58, 105]

4.3.4 Outcome variable

The outcome variable was an overall survival in months (defined as interval between metastatic breast cancer diagnosis and death or study end point). The study ascertained the occurrence of death in two ways. For in-hospital deaths, the hospital record was reviewed. For out of hospital deaths, the data were confirmed utilizing U.S. social security death index. Analyses censored all followed on June 30, 2008.

4.3.5 Statistical analysis

Simple imputation procedure for missing data used SPSS implementation of the Expectation Maximization (EM) algorithm of Dempster, Laird and Rubin (1977).[106] The

frequency distribution of complete data of variables which were imputed was compared to the available data of corresponding variables prior to imputation using appropriate two sample t-tests for continuous variables and chi-squared statistics for categorical variables.

Log rank test and Kaplan-Meier's curve for categorical variables were conducted to evaluate the relationship between independent variables and outcome of interest. Cox proportional hazards regression model was performed for univariate and multivariate analysis to produce hazard ratios (HRs) and 95% confidence interval (95% CI).

Multicollinearity was assessed by using coefficient of multiple determination (R^2), tolerance, and variance-inflation factor (VIF) for each independent variable using remaining covariates as its predictors; no serious multicollinearity was identified. Two tailed p-value less than 0.05 was considered significant. SAS (version 9.2) and SPSS (version 17.0) were used.

4.4 RESULTS

Analysis included 557 patients with metastatic breast cancer diagnosed between January 1, 1999 and June 30, 2008. The median survival length was 40 months (range 1-114 months), with 269 (48.3%) alive and 288 (51.7%) dead. The characteristics of 557 patients are summarized in table 5. The median age was 55 years (range 26-88 years). The majority of patients was non-black (93.5%), post menopausal (74.5%), Charlson comorbidity condition-free (79.5%), ER/PR positive (73.2%), HER2 negative (65.5%), and metastatic at only one site (61.8%). The median household income was $41,335 (range $18,473-$85,102) and 287 (51.5%) patients had more than high school education.

Half of the patients (n = 237, 42.5%) had a history of hypertension. Most patients (73.2%) were overweight (n = 257, 46.1%) or obese (n = 151, 27.1%), while other patients were of normal weight range (n = 118, 21.2%) or underweight group (n = 31, 5.6%). 114 (20.5%) patients had one or more of the Charlson comorbidity conditions: mainly diabetes (6.6%), mild liver disease (4.3%), chronic pulmonary disease (CPD, 4.1%) and congestive heart failure (CHF, 2.3%). Bone, liver, brain metastasis were diagnosed in 301 (54.0%), 116 (20.8%), and 34 (6.1%) patients, respectively.

4.4.1 Univariate analysis

Table 6 and Figure 3-9 showed results for univariate analyses of survival after breast cancer metastasis. Patients with metastatic breast cancer had significantly unfavorable outcomes when they were older (P = 0.003), having less than or equal high school education (P = 0.034). A history of hypertension (P < 0.0001), ER/PR negative (P = 0.001) and HER2 negative (P = 0.048), were significantly associated with poor survival after breast cancer metastasis. In addition, patients diagnosed with greater number of metastatic sites (P < 0.0001), brain metastasis (P = 0.009) or liver metastasis (P = 0.005) had significantly worse prognoses. Charlson comorbidity score (P = 0.059) for one unit increase and the normal body weight group (P = 0.068) compared to the underweight group had a marginal negative effect on survival. Race, menopausal status, CHF, CPD, mild liver disease, diabetes, metastasis at bone or other site did not significantly impact survival.

4.4.2 Multivariate analysis

A multivariate analysis was performed including all variables in univariate analysis (Table 7). In multivariate analysis, the normal body weight group (HR 1.86, 95% CI 1.03-3.35) had significantly poorer survival outcomes than the underweight group. History of hypertension (HR 1.53, 95% CI 1.14-2.07), ER/PR negative status (HR 1.84, 95% CI 1.40-2.41), HER2 negative status (HR 1.45, 95% CI 1.09-1.93), and greater number of metastatic sites (HR 1.27, 95% CI 1.01-1.59) were found to be unfavorable factors on survival. Age, education and brain or liver metastasis, which were significant prognostic factors on survival in univariate analysis, were not strongly associated with survival after adjustment for other covariates in multivariate analysis.

There was a synergistic interaction (P = 0.019) between brain and liver metastasis negatively influencing survival. We performed the univariate and multivariate analysis with independent variables using the parametric, accelerated failure-time models assuming a Weibull distribution [107] and results were comparable to those in univariate and multivariate analysis using Cox regression models (data not shown).

4.5 DISCUSSION

The present study was a hospital clinic-based retrospective study evaluating potential factors including socioeconomic, clinical, and pathological factors related to survival among 557 women with metastatic breast cancer. The study found that a history of hypertension, ER/PR status, HER2 status, number of metastatic sites, and BMI at the time of diagnosis with metastatic breast cancer had significant impact on survival in

multivariate analysis, while age, education, brain or liver metastasis were strong predictors on survival in univariate analysis only.

The majority of the breast cancer literature suggests that higher BMI (obese or overweight) at diagnosis is associated with a poor prognosis [19-23], which is consistent with the present study showing that over weight and obese patients had worse survival than underweight patients in univariate analysis. In the present study, the normal body weight at metastatic diagnosis was found to have almost double risk of dying after metastatic breast cancer than a patients' underweight status. The weight loss of over 10% after breast cancer diagnosis increased the risk of breast cancer mortality compared to being weight stable [11, 71], and this risk was more pronounced among women who were obese (BMI $\geq$ 30kg/m^2) before diagnosis.[20] We attempted to evaluate the effect of weight change from breast cancer to metastatic diagnosis on survival, however, weight change was not included in the data analysis due to the high level of missing data. It is reasonable to assume that patients who lose weight between initial breast cancer diagnosis and metastasis have poor survival.

The number of metastatic sites was a major prognostic factor for survival after adjustment for other covariates. This finding validates previous work that found more metastatic sites at diagnosis a poor prognosis.[10, 11, 64, 79, 84] Bone metastasis was associated with a relatively better survival [71, 75, 78, 108] and bone is the most frequent site of metastasis with 54% in our study and 40-55% in other studies.[8, 76] As previously reported, the association between brain or liver metastases and low survival rate was observed significantly in only univariate analysis in consistency with other studies.[11, 17, 64] When lung, liver and other visceral sites were all combined in the variable "visceral dominant

site", they have been reported to be influential factors on poor breast cancer survival.[7, 8, 75, 77, 81, 84]

This study demonstrated that patients with positive HER2 status had better survival which is in concordance with other studies.[9, 75] Several studies showed that ER and/or PR negative increased the risk of poor response to treatment or mortality among metastatic breast cancer patients.[7, 8, 64, 75-81] The peak hazard of mortality in ER-positive tumors occurred later than in ER-negative tumors. Grasic et al. reported that the difference of breast cancer mortality risk between ER-negative and ER-positive occurred from 5 year on, and the hazard in ER-positive was higher than ER-negative.[82] Adjuvant hormonal treatment with tamoxifen diminishes the risk for relapse and death in ER-positive tumors, and the relative gain of mortality in tamoxifen treated compared to non-treated group increased at 5 years.[83] Our findings are similar to the previous study results by reporting that ER/PR positive had better impact on 5 year survival after breast cancer metastasis, afterwards the risk of ER/PR-positive increased on survival.

Comorbidity affects medical decision-making, outcomes in terms of treatment complications, recurrence, and survival in breast cancer patients. Unlike other reports [24-30], our study did not observe a significant association between comorbidity and survival. Our chart abstraction procedure detected Charlson comorbidity in only 21% of cases. Most other studies reported a higher prevalence of Charlson comorbidity (37-65%).[24, 28-30]

Consistent with another study [28], we observed an association between history of hypertension and survival after diagnosis of metastatic breast cancer even after adjustments for other comorbidities. Hypertension can be an important risk factor for cancer. For example, cell death by apoptosis can influence the growth of vascular smooth

muscle cells (VSMCs) and the increased proliferation of VSMCs responds exaggeratedly to growth stimuli, which is characterized by shortening of the cell cycle. This mechanism may lead to increased cellular proliferation.[57] The Charlson list of comorbidities excludes hypertension. Future studies of clinical predictors of survival after breast cancer diagnosis should not rely only on Charlson comorbidities, but also include, at minimum, a history of hypertension.

This study had limitations. We did not consider specific treatment regimens in the analysis to preserve the power due to high degree of variation in treatment regimens among metastatic breast cancer women. However, it is reasonable to assume that treatments were selected in accordance with acceptable criteria and were carried out by competent physicians at this university affiliated, National Cancer Institute (NCI) designated site.

Given that the median survival length (18 months) of patients with unavailable charts was significantly shorter than that (40 months) of patients having complete data, the possible sources of selection bias can not be excluded. We can assume that paper-version medical records for patients who died earlier have higher chance of being lost than those for patients who died recently. The exclusion of patients whose charts were not found from the analysis did not appear to make significantly different changes in study results in terms of analyses of age, race, number of metastatic sites, metastatic location, ER/PR status and HER2 status.

Our data collection procedure extracted comorbidity information from multiple medical record sources (Figure 2), including clinic intake forms, progress notes, laboratory results, and physician summaries. Medical record documentation was not

strictly uniform over the period of time (January 1, 1999 through June 30, 2008) covering first diagnosis of metastatic breast cancer. For example, medical records for women with breast cancer metastasis diagnosed during an early time period more often lacked a clinic intake form than medical records for women diagnosed during a later time period (data not shown). This type of calendar time-related variability in medical record completeness or quality may have introduced a systemic error leading to 1) the underestimation of Charlson comorbidity during early time periods and 2) the failure to detect association between Charlson comorbidity and survival because of concurrent improvements in the effectiveness of medical treatment for metastatic breast cancer. In our study, however, Charlson comorbidity score values were independent of the year of first diagnosis of metastatic breast cancer (data not shown). Assuming similarly ill women were diagnosed with metastatic breast cancer in earlier and later time periods, this result suggests that variable medical record quality did not adversely affect our results associating the Charlson comorbidity measurements with survival.

We did the sensitivity test using available data of variables prior to imputation procedure compared to complete data of corresponding variables which were imputed, and there was no apparent difference in the frequency distribution and in the univariate analysis. In addition, our study findings are fairly robust since similar results using semi-parametric, Cox regression and parametric, accelerated failure-time models were obtained.

In conclusion, studies of prognostic factors in metastatic breast cancer patients vary considerably in terms of the patients' selection, availability of clinical, socio-economical, biological covariates, patients' lost follow-up, and statistical method for

analysis.[8] Many studies have considered individual risk factor, one at a time, but few studies have considered a comprehensive range of risk factors together.

Utilizing a large database reflective of current metastatic breast cancer treatment this study employed a uniform protocol for data collection and examined prognostic factors in a comprehensive fashion. The present study findings may form a foundation for the growing corpus of knowledge explaining the outcome differences in treatment of patients with metastatic breast cancer, potentially helping to create more personalized treatment approaches for this vulnerable group.

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4.7 TABLES AND FIGURES

Table 5. Characteristics of patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Variable*	Number of patients	Percentage
Age (Median age in years 55years)		
26-88 years	557	100
Ethnicity		
Non-Black	521	93.5
Black	36	6.5
Education		
≤ High School	270	48.5
> High School	287	51.5
Median Household Income (Median of Median Household Income $ 41,335)		
$18,473-$85,102	557	100
BMI		
<20 kg/m^2	31	5.6
20-24.9 kg/m^2	118	21.2
25-29.9 kg/m^2	257	46.1
≥30 kg/m^2	151	27.1
Menopausal status		
Pre menopause	142	25.5
Post menopause	415	74.5
History of hypertension		
No	320	57.5
Yes	237	42.5
Charlson comorbidity score		
0	443	79.5
1	15	2.7
2	32	5.7
3+	67	12.1
Charlson Comorbidity Condition		
Congestive heart failure	13	2.3
Chronic pulmonary disease	23	4.1
Mild liver disease	24	4.3
Diabetes	37	6.6
ER/PR status		
ER/PR positive	408	73.2
ER/PR negative	149	26.8
HER2 status		
HER2 positive	192	34.5
HER2 negative	365	65.5

Table 5 (Continued)

Variable	Number of patients	Percentage
Number of metastatic sites		
1	344	61.8
2	137	24.6
3+	76	13.6
Metastatic location		
Brain	34	6.1
Bone	301	54.0
Liver	116	20.8
Other	309	55.5

Abbreviation: BMI, body mass index; ER/PR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor-2.

* Variables with < 1% of frequency were excluded from analysis.

Table 6. Univariate analysis with Cox regression in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Variable**	Patients no (%)	Hazard ratio	95% CI	P-value
Age	557 (100)	1.01	1.01-1.02	0.003
Ethnicity				
Non-Black	521 (93.5)	1.00	referent	
Black	36 (6.5)	1.46	0.88-2.43	0.144
Education*				
≤ High School	270 (48.5)	1.00	referent	
> High School	287 (51.5)	0.78	0.62-0.98	0.034
BMI*				0.012†
<20 kg/m^2	31 (5.6)	1.00	referent	
20-24.9 kg/m^2	118 (21.2)	1.71	0.96-3.03	0.068
25-29.9 kg/m^2	257 (46.1)	1.10	0.63-1.91	0.736
≥30 kg/m^2	151 (27.1)	1.46	0.82-2.57	0.196
Menopausal status*				
Pre menopause	142 (25.5)	1.00	referent	
Post menopause	415 (74.5)	1.17	0.89-1.52	0.256
History of hypertension*				
No	320 (57.5)	1.00	referent	
Yes	237 (42.5)	1.62	1.28-2.06	<0.0001
Charlson comorbidity score	557 (100)	1.09	1.00-1.18	0.059
Congestive heart failure				
No	544 (97.7)	1.00	referent	
Yes	13 (2.3)	1.86	0.88-3.96	0.105
Chronic pulmonary disease				
No	534 (95.9)	1.00	referent	
Yes	23 (4.1)	1.30	0.77-2.19	0.319
Mild liver disease				
No	533 (95.7)	1.00	referent	
Yes	24 (4.3)	1.35	0.75-2.41	0.315
Diabetes				
No	520 (93.4)	1.00	referent	
Yes	37 (6.6)	1.34	0.84-2.13	0.223
ER/PR status				
ER/PR positive	408 (73.2)	1.00	referent	
ER/PR negative	149 (26.8)	1.54	1.20-1.98	0.001
HER2 status				
HER2 positive	192 (34.5)	1.00	referent	
HER2 negative	365 (65.5)	1.28	1.00-1.64	0.048
Number of metastatic sites	557 (100)	1.37	1.21-1.56	<0.0001

Table 6 (Continued)

Variable**	Patients no (%)	Hazard ratio	95% CI	P-value
Metastatic location				
Brain				
No	523 (93.9)	1.00	referent	
Yes	34 (6.1)	1.77	1.16-2.72	0.009
Bone				
No	256 (46.0)	1.00	referent	
Yes	301 (54.0)	1.20	0.95-1.51	0.136
Liver				
No	441 (79.2)	1.00	referent	
Yes	116 (20.8)	1.47	1.13-1.93	0.005
Other				
No	248 (44.5)	1.00	referent	
Yes	309 (55.5)	1.02	0.81-1.29	0.847

Abbreviation: 95% CI, 95% Confidence Interval; BMI, body mass index; ER/PR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor-2.

* Missing data were replaced with imputed data using simple imputation procedure of EM algorithm.[106]

** Variables with P value≈1.0 or with < 1% of frequency were excluded from analysis.

† P-value for omnibus test.

Table 7. Multivariate analysis with Cox regression in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Variable	Patients no (%)	Hazard ratio	95% CI	P-value
Age	557 (100)	1.01	1.00-1.03	0.134
Ethnicity				
Non-Black	521 (93.5)	1.00	referent	
Black	36 (6.5)	1.20	0.69-2.08	0.528
Education*				
≤ High School	270 (48.5)	1.00	Referent	
> High School	287 (51.5)	0.87	0.68-1.12	0.282
BMI*				0.025†
<20 kg/m^2	31 (5.6)	1.00	referent	
20-24.9 kg/m^2	118 (21.2)	1.86	1.03-3.35	0.040
25-29.9 kg/m^2	257 (46.1)	1.20	0.67-2.15	0.544
≥30 kg/m^2	151 (27.1)	1.35	0.74-2.46	0.335
Menopausal status*				
Pre menopause	142 (25.5)	1.00	referent	
Post menopause	415 (74.5)	0.82	0.57-1.17	0.277
History of Hypertension*				
No	320 (57.5)	1.00	referent	
Yes	237 (42.5)	1.53	1.14-2.07	0.005
Charlson comorbidity score	557 (100)	0.97	0.84-1.12	0.699
Congestive heart failure				
No	544 (97.7)	1.00	referent	
Yes	13(2.3)	1.20	0.49-2.91	0.694
Chronic pulmonary disease				
No	534 (95.9)	1.00	referent	
Yes	23 (4.1)	1.37	0.73-2.58	0.323
Mild liver disease				
No	533 (95.7)	1.00	referent	
Yes	24 (4.3)	1.28	0.66-2.48	0.459
Diabetes				
No	520 (93.4)	1.00	referent	
Yes	37 (6.6)	1.25	0.67-2.34	0.490
ER/PR status				
ER/PR positive	408 (73.2)	1.00	referent	
ER/PR negative	149 (26.8)	1.84	1.40-2.41	<0.0001
HER2 status				
HER2 positive	192 (34.5)	1.00	referent	
HER2 negative	365 (65.5)	1.45	1.09-1.93	0.010
Number of metastatic sites	557 (100)	1.27	1.01-1.59	0.043

Table 7 (Continued)

Variable	Patients no (%)	Hazard ratio	95% CI	P-value
Metastatic location				
Brain				
No	523 (93.9)	1.00	referent	
Yes	34 (6.1)	1.54	0.91-2.62	0.109
Bone				
No	256 (46.0)	1.00	referent	
Yes	301 (54.0)	1.32	0.91-1.90	0.146
Liver				
No	441 (79.2)	1.00	referent	
Yes	116 (20.8)	1.37	0.94-1.99	0.100
Other				
No	248 (44.5)	1.00	referent	
Yes	309 (55.5)	1.01	0.66-1.53	0.983

Abbreviation: 95% CI, 95% Confidence Interval; BMI, body mass index; ER/PR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor-2.

* Missing data were replaced with imputed data using simple imputation procedure of EM algorithm.[106]

† P-value for omnibus test.

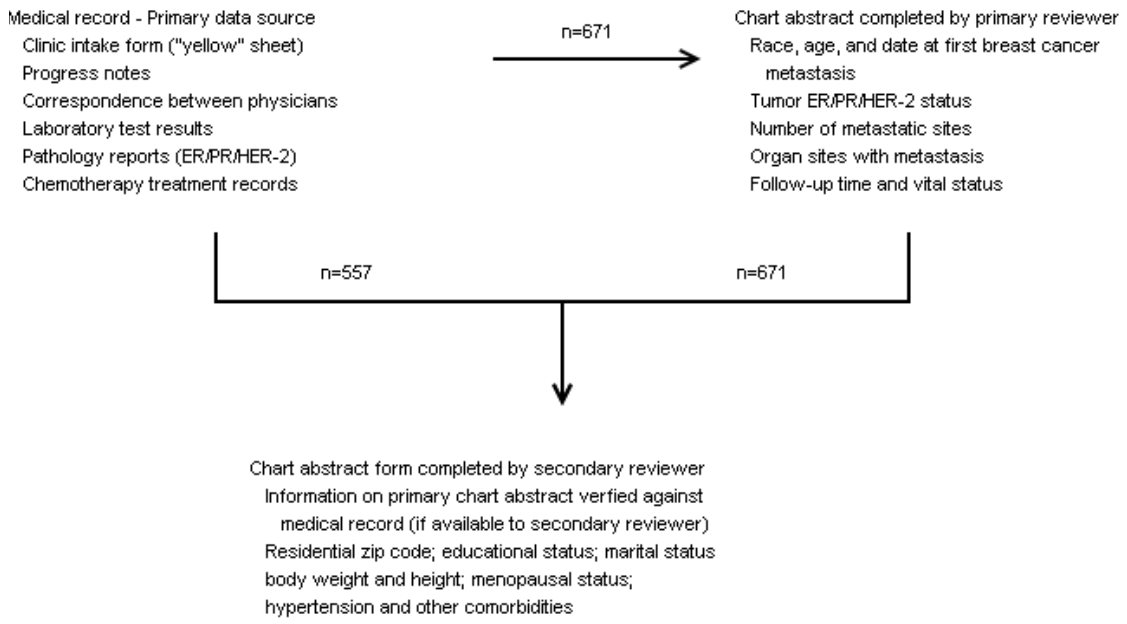

Figure 2. Medical record abstraction procedure

Education

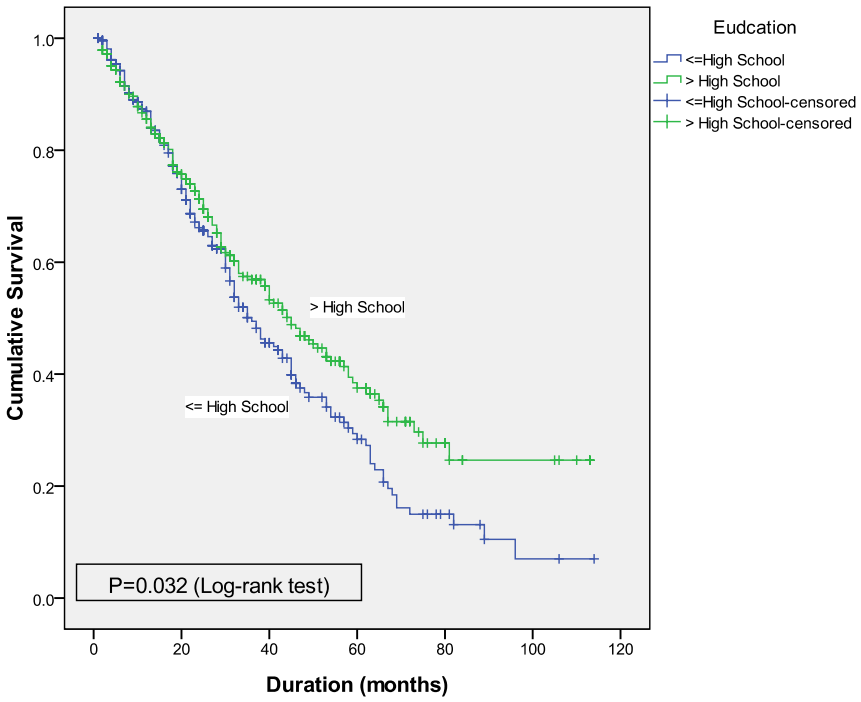

Figure 3. Kaplan-Meier's curve of survival by education with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

BMI

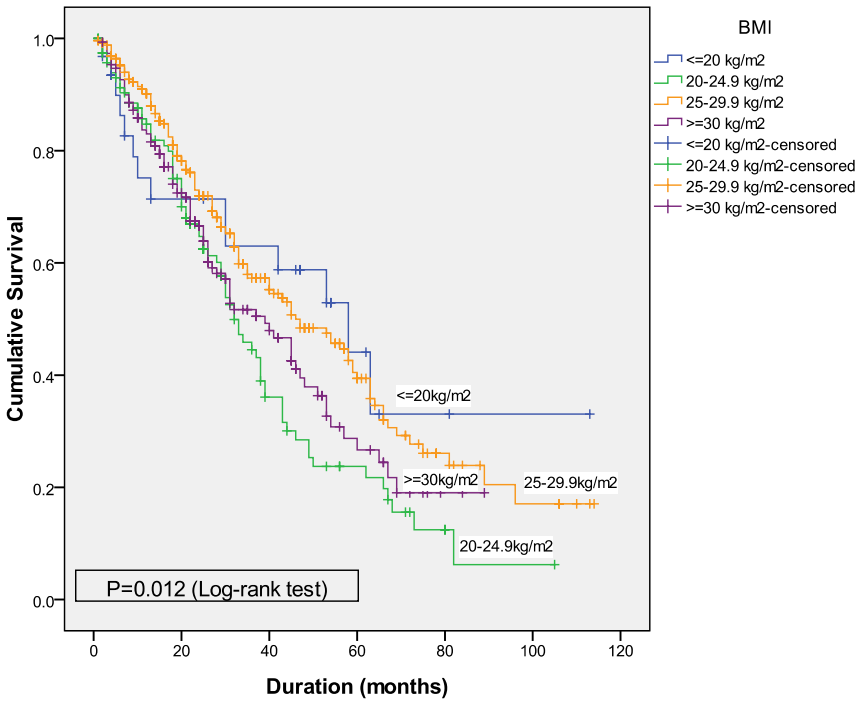

Figure 4. Kaplan-Meier's curve of survival by BMI with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

History of hypertension

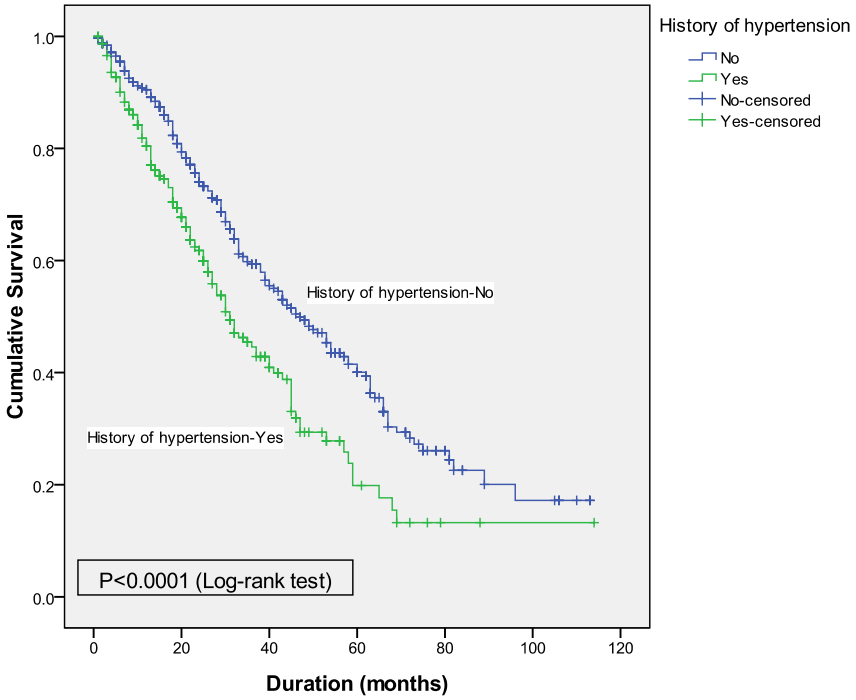

Figure 5. Kaplan-Meier's curve of survival by history of hypertension with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

ER/PR status

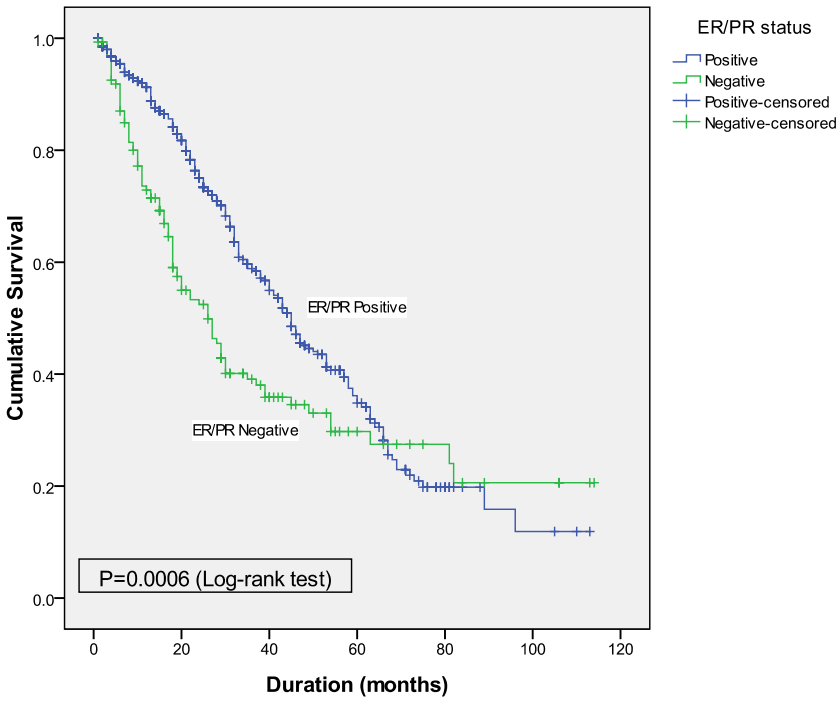

Figure 6. Kaplan-Meier's curve of survival by ER/PR status with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

Her2 status

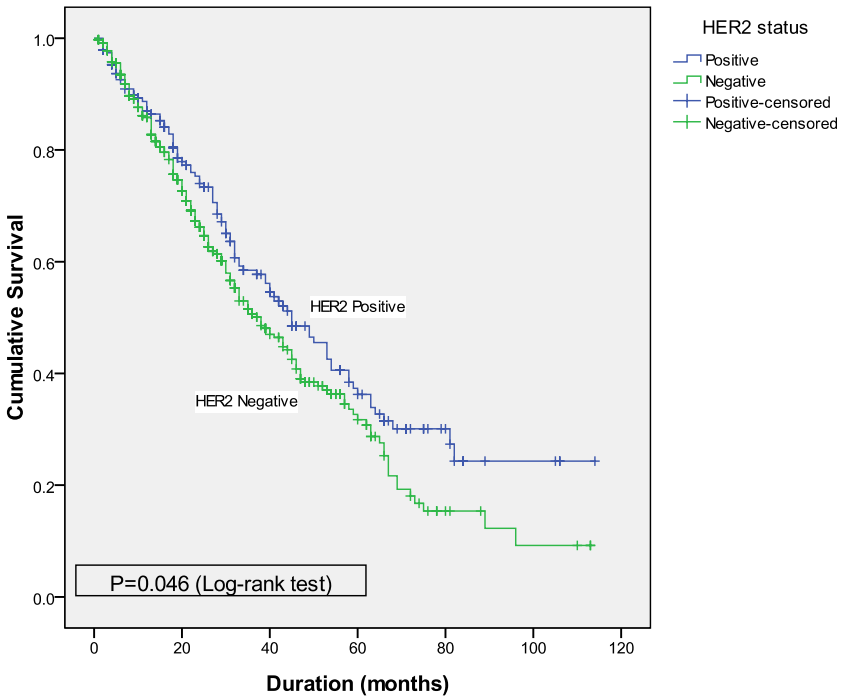

Figure 7. Kaplan-Meier's curve of survival by HER2 status with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

Brain metastasis

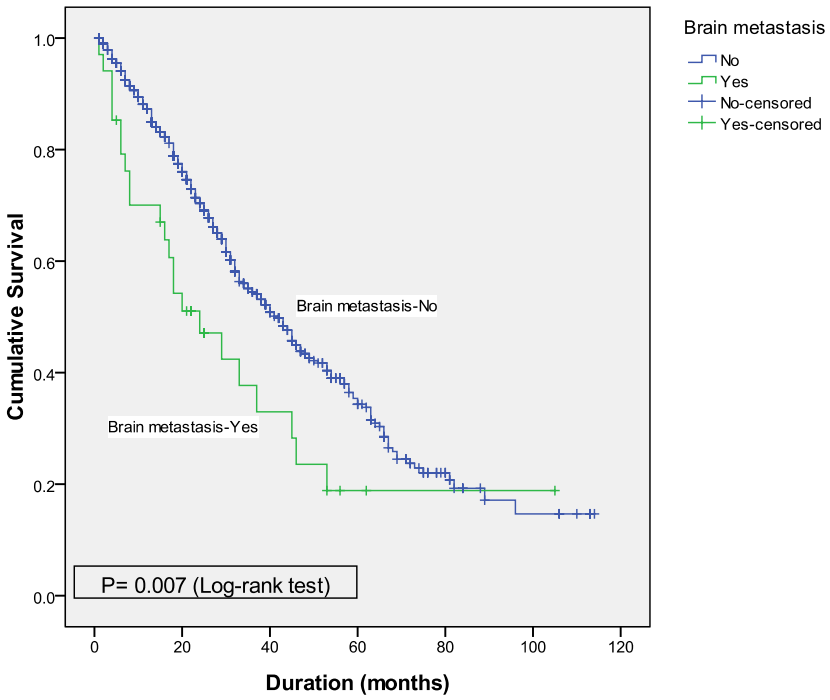

Figure 8. Kaplan-Meier's curve of survival by brain metastasis with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

Liver metastasis

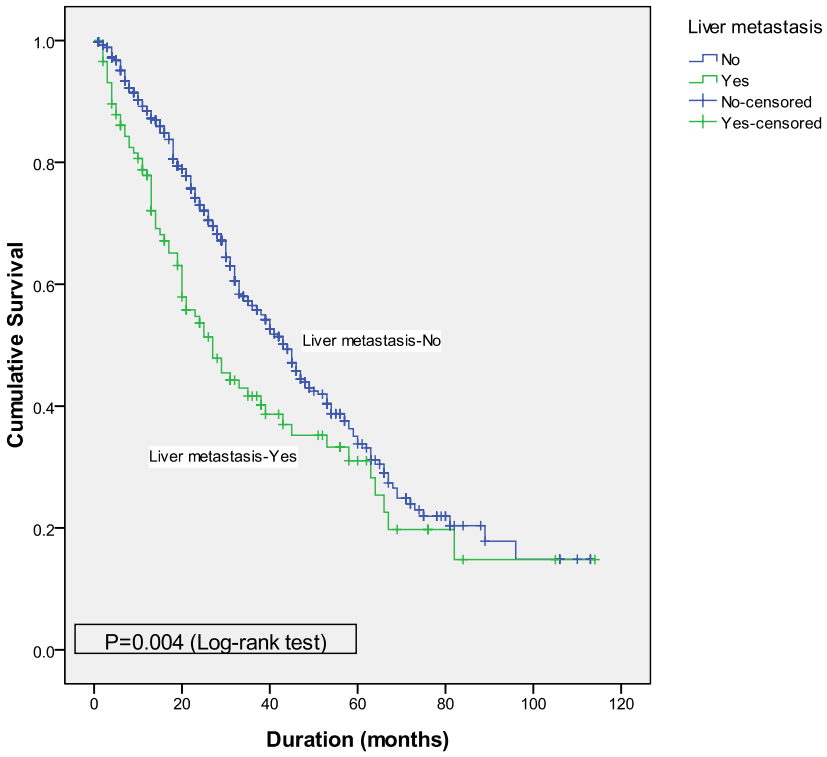

Figure 9. Kaplan-Meier's curve of survival by Liver metastasis with log-rank test in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program (Categorical covariates significantly influencing on survival in univariate analysis were presented.)

5.0 THE EFFECT OF DELAYS IN TREATMENT FOR BREAST CANCER METASTASIS ON SURVIVAL

To be submitted for publication

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Running Title: Delays in treatment for breast cancer metastasis

5.1 ABSTRACT

Background: It is generally accepted that delay in receiving treatment for breast cancer results in adverse prognostic outcomes. The purpose of the present study was to evaluate the impact of delay in treatment after the diagnosis of metastatic disease on survival measured from metastatic breast cancer diagnosis and from first treatment while controlling for immortal time effect among patients with metastatic breast cancer.

Populations and Methods: A total of 553 patients with the initial breast cancer metastasis diagnosis from one large urban practice have been followed up between January 1, 1999 and June 30, 2008. Prognostic factors and outcomes of these patients were analyzed by using log-rank test and Cox regression model. Backward stepwise selection of covariates was conducted to assess the association of treatment delay with survival.

Results: The median survival was 40 months (range 1-114 months), with 265 (47.9%) alive and 288 (52.1%) dead at the end of the follow-up period. Treatment delays of > 12 week had worse survival from first treatment than the delays of 4-12 week in univariate analysis (HR 2.02, 95% CI 1.16-3.54), and had a marginal impact on poor survival in multivariate analysis (HR 1.76, 95% CI 0.99-3.13). Moreover, the interval of 12-24 week, compared to the interval of 4-12 week was a prognostic factor for survival from first treatment in multivariate analysis (HR 2.39, 95% CI 1.19-4.77).

Conclusion: This study demonstrated that delay of over 12 weeks in receiving treatment for metastatic breast cancer results in adverse survival outcomes. Findings of this study suggest the usefulness of targeted efforts to ensure prompt treatment initiation in patients diagnosed with metastatic breast cancer.

Key words: advanced breast cancer, treatment delay

5.2 INTRODUCTION

Breast cancer is the most common cancer in women in the United States and in other industrialized countries, and the second leading cause of death for women with cancer.[100] Despite improved techniques for breast cancer screening, as many as 7% of women present with metastatic disease at the time of diagnosis.[101] While most women are diagnosed at an early stage, 20% to 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.[102] Survival time for patients with metastasis varies greatly with median survival duration ranging from less than 9 months to over 3 years.[7]

Delays in the initiation of breast cancer treatment may adversely affect survival. The influence of delays on survival between breast cancer diagnosis and treatment remains controversial. Several studies observed that survival was worse among patients with longer treatment delays [31, 43, 86-91]; others did not show that survival was affected by treatment delay interval.[34-42] These conflicting results may be explained by differences in the patients' selection, by difference in the cut-offs used to define delay, and by availability of clinical, socio-economical and biological covariates.[43] One of the major limitations with the majority of previous studies on the effect of delays on survival is that no account has been taken of immortal time effect. Immortal time refers to a span of time in the follow-up period of a cohort during which an outcome of interest could not

possibly occur.[109-111] Measurement of survival from the date of treatment for the effect of treatment delays on survival can overcome immortal time bias.

This study aimed to evaluate the impact of delays in the initiation of treatment on survival from metastatic breast cancer diagnosis and from first treatment in patients with metastatic breast cancer. To our knowledge, this is the first study to analyze the effect of treatment delays on survival among metastatic breast cancer patients. Moreover, this study controlled for immortal time bias by measuring survival from the initiation of treatment. The study used data from 553 patients with metastatic breast cancer seen at one large urban practice between January 1, 1999 and June 30, 2008.

5.3 POPULATIONS AND METHODS

5.3.1 Patients Selection

The study included 553 patients with the first breast cancer metastasis seen at two urban hospitals (Montefiore and Magee) of the University of Pittsburgh Medical Center (UPMC) and by the University of Pittsburgh Cancer Institute (UPCI) Breast Cancer Program physicians. Patients with metastatic breast cancer were identified from daily hospital clinic lists and confirmed with medical records through clinical, radiological, or pathologic exams. Inclusion criteria included female patients aged eighteen 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 excluded because their medical records were unavailable for the secondary review.

Additionally, 4 patients were excluded because they did not have history of clinic follow-up (i.e., missing information for treatment) prior to the first treatment or until study end point. This study was approved by the University of Pittsburgh Institutional Review Board.

5.3.2 Data Collection

The medical record abstraction protocol was developed (Figure 10). Retrospective review of medical records according to study protocol was utilized. Chart abstraction form was summarized monthly by trained registered nurse. The primary data sources for abstraction were hand written medical records, usually completed at the monthly patient visit.

Age, race, estrogen receptor (ER) and/or progesterone receptor (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 primary reviewer. Quality guaranteed protocol for the secondary chart review was established. The weighted kappa coefficients of secondary chart abstraction with n = 23, and of repeated chart abstraction with n = 23 for Charlson comorbidity score were 0.88 (95% CI 0.64-1.00) and 0.88 (95% CI 0.66-1.00), respectively; secondary and repeated chart abstraction for hypertension were 0.93 (95% CI 0.79-1.00) and 1.00 (95% CI 1.00-1.00), respectively.

The secondary chart retrieval procedure was performed to evaluate marital status, socioeconomic status (SES) including insurance, education, residential zip code, BMI at

breast cancer diagnosis and at study entry, weight change (difference weight between at metastasis and weight at breast cancer diagnosis), menopausal status, and comorbidities according to the protocol. All predictor variables were measured at the time of metastatic breast cancer.

Variables with more than 40% missing data such as marital status, insurance, BMI at breast cancer diagnosis and weight change were excluded for purposes of the analysis. Missing data imputation procedure was accomplished on education, median household income, BMI (at study entry), menopausal status and hypertension having missing values ranged 5% to 35% (hypertension 5%, menopause 11%, education 13%, BMI 20%, income 35%).

5.3.3 Definition of treatment delay

Treatment delay was defined as the time in days between the date of initial breast cancer metastasis and the date of the initiation of first treatment. The date of first metastatic breast cancer diagnosis was identified as the date of first metastatic biopsy or CT scan, whichever came first. The date of first treatment initiation was considered as the date of the start of first treatment obtained from paper-version medical records. Treatment types included systematic therapy such as chemotherapy, hormonal therapy, immunologic therapy, vaccine therapy, and other biologic therapy. Fourteen patients did not have a history of treatment until death or end of study period. Their treatment delay interval was censored at the date of death, or study end point.

Week (7 days) was chosen as a unit of time in this study. Period lasting for less than 7 days was recorded as "0 week". Treatment delay interval was categorized in two ways: 1) categorization into 3 groups (less than or equal to 4 weeks, more than 4 weeks to less than or equal to 12 weeks, and more than 12 weeks); 2) categorization into 4 groups (less than or equal to 4 weeks, more than 4 weeks to less than or equal to 12 weeks, more than 12 weeks to less than or equal to 24 weeks, and more than 24 weeks) to keep lead time effect to a minimum.[85] Lead time bias can be kept to a minimum by excluding patients having delays of >24 weeks, and by comparing the effect of delays between 4-12 week and 12-24 week on survival.[85] The categorizations of treatment delay interval were similar to the ones previously used in other similar studies [34, 43, 88], especially the meta-analysis conducted by Richards et al.[85]

5.3.4 Predictor variables

Demographic or socioeconomic variables included age, race, education, median household income, BMI, and menopausal status. The median household income was linked to residential zip code matched to U.S. 2000 census summary file 3.[103] The BMI was calculated as a weight in kilogram (kg) divided by a height in meters squared and classified into four groups: less than 20kg/m^2 (underweight), 20-24.9kg/m^2 (normal), 25-29.9kg/m^2 (overweight), 30kg/m^2 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 used the pathologic report following the first metastatic site biopsy, if

available, and the initial breast cancer site biopsy, otherwise. Metastatic locations were categorized into four 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.

Clinical variables included a history of hypertension, Charlson comorbidity conditions, and Charlson comorbidity score. Hypertension was defined as a blood pressure greater than or equal to 140 mmHg systolic pressure or greater than or equal to 90 mmHg diastolic pressure (American Heart Association) [104], at least twice presented at different visits. Hypertension included controlled hypertension. The Charlson comorbidity score, a composite of 19 comorbidity conditions was constructed using 18 comorbidity conditions (without metastatic solid tumor) which were weighted by 1, 2, 3, or 6. The sum of the weighted comorbidity conditions has a theoretical range between 0 and 31. Final Charlson comorbidity score was obtained by adding the age-comorbidity combined risk score.[58, 105]

5.3.5 Outcome variable

The outcome variable was an overall survival in months defined into two ways: interval between metastatic breast cancer diagnosis and death or study end point; interval from the date of first treatment to the date of death or the end of follow-up period. Fourteen patients who were either censored or died before first treatment were excluded from analysis for the effect of treatment delays on survival from first treatment. The study

ascertained the occurrence of death in two ways. For in-hospital deaths, the hospital record was reviewed. For out of hospital deaths, the data were confirmed utilizing U.S. social security death index. Analyses censored all followed on June 30, 2008.

5.3.6 Statistical analysis

Simple imputation procedure for missing data used SPSS implementation of the Expectation Maximization (EM) algorithm of Dempster, Laird and Rubin (1977).[106] The frequency distribution of complete data of variables which were imputed was compared to the available data of corresponding variables prior to imputation using appropriate two sample t-tests for continuous variables and chi-squared statistics for categorical variables.

Multicollinearity was assessed by using coefficient of multiple determination (R^2), tolerance, and variance-inflation factor (VIF) for each predictor variable using remaining covariates as its predictors; no serious multicollinearity was identified.

Demographic, pathological, and clinical characteristics according to the length of treatment delays were tested using F-test from Analysis of Variance for continuous variables and chi-squared statistics for categorical variables. If continuous variables were skewed or had outliers, Kruskal-Wallis test was implemented.

Log rank test for categorical variables was conducted to evaluate the relationship between predictor variables and survival. Kaplan-Meier estimation was used to generate group-specific survival curves for treatment delay categories. Cox proportional hazards regression model was performed for univariate analysis for both categorical and continuous variables to produce hazard ratios (HRs) and 95% confidence interval (95%

CI). Cox regression using backward stepwise selection of covariates was accomplished to assess the association of treatment delays with survival, accounting for covariates.

Two tailed p-value of less than 0.05 was considered significant. SAS (version 9.2) and SPSS (version 17.0) were used.

5.4 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 265 (47.9%) women having survived and 288 (52.1%) having died. Of the 553 patients included in the analysis, majority of patients was non-black (93.5%), post menopausal (74.9%), Charlson comorbidity condition-free (79.4%), ER/PR positive (73.1%), HER2 negative (65.5%), and had metastasis at only one site (61.5%). The median age was 55 years (range 26-88 years). The median household income was $41,190 (range $18,473-$85,102) and 283 (51.2%) patients had more than high school education. Most patients (73.1%) were overweight (n = 253, 45.8%) or obese (n = 151, 27.3%), while other patients were of normal weight or underweight group (n = 149, 26.9%). Half of the patients (n = 237, 42.9%) had a history of hypertension, and 114 (20.6%) patients had one or more of the Charlson comorbidity conditions. Bone, liver, and brain metastasis were diagnosed in 298 (53.9%), 116 (21.0%), and 34 (6.1%) patients, respectively.

The characteristics of 553 patients by the length of treatment delays (≤ 4 week, 4-12 week, and > 12 week) are summarized in table 8. The median treatment delay interval

was 13 days (25 percentile 0 day and 75 percentile 32 days). Patients having treatment delays more than 4 weeks were more likely to have brain metastasis (P = 0.0006) and ER/PR negative status (P < 0.0001). More than two site metastases (P = 0.013), and other metastasis (i.e., including soft tissue, lymph node, and visceral site) (P = 0.002) were more likely to be found in patients having treatment delays with 4-12 week. Age was related to the increase of treatment delays (P = 0.047). No other differences of characteristics by treatment delays were noted.

5.4.1 Univariate Analysis

Table 9 outlines results for univariate analyses of survival after breast cancer metastasis. Patients with metastatic breast cancer had significantly unfavorable outcomes when they were older (P = 0.004), having less than or equal to high school education (P = 0.0495), history of hypertension (P = 0.0001), ER/PR negative (P = 0.002), and HER2 negative (P = 0.047). In addition, patients diagnosed with greater number of metastatic sites (P < 0.0001), brain metastasis (P = 0.014) or liver metastasis (P = 0.006) had significantly worse prognoses. Charlson comorbidity score (P = 0.067) for one unit increase and the normal body weight group (P = 0.069) compared to the underweight group had a marginal negative effect on survival. Race, menopausal status, congestive heart failure (CHF), chronic pulmonary disease (CPD), mild liver disease, diabetes, metastasis at bone or other site did not significantly impact survival.

5.4.2 The effect of treatment delays on survival

Survival graphs of treatment delays (≤ 4 week, 4-12 week, and > 12 week) related to survival since metastatic breast cancer diagnosis and since first treatment were presented in Figure 11 and Figure 12, respectively.

Table 10 showed results for univariate and multivariate analyses of treatment delays (≤ 4 week, 4-12 week, and > 12 week) on survival after breast cancer metastasis. The treatment delay interval of > 12 week was not associated with survival relative to metastatic breast cancer diagnosis, compared to the 4-12 week of treatment delays in univariate and multivariate analysis.

Cox regression analyses of treatment delays (≤ 4 week, 4-12 week, and > 12 week) on survival after first treatment were conducted (Table 11). Treatment delays of > 12 week had worse survival from first treatment than the interval of 4-12 week in univariate analysis (HR 2.02, 95% CI 1.16-3.54), and had a marginal impact on poor survival in multivariate analysis (HR 1.76, 95% CI 0.99-3.13). The treatment interval of ≤ 4 week was not significantly related to survival relative to first treatment using 4-12 week of treatment delays as a referent group in univariate and multivariate analysis.

Additionally, history of hypertension (HR 1.64, 95% CI 1.26-2.13), ER/PR negative status (HR 1.70, 95% CI 1.27-2.27), HER2 negative status (HR 1.63, 95% CI 1.24-2.15), greater number of metastatic sites (HR 1.32, 95% CI 1.15-1.51), were found to be unfavorable factors on survival from first treatment. Liver metastasis was associated with survival on borderline (HR 1.32, 95% CI 0.98-1.79). The normal body weight group (HR 2.12, 95% CI 1.16-3.90) was related to poorer survival than the underweight group (data not shown). There were no significant interaction terms between predictor variables

and treatment delays on survival relative first treatment. Similar results for multivariate analyses of covariates related to survival from breast cancer metastasis were observed (date not shown).

Furthermore, treatment delay interval (classified as ≤ 4 week, 4-12 week, 12-24 week, and > 24 week) was assessed for the effect of delays of 12-24 week, compared to 4-12 week on survival. The interval of 12-24 week had poor survival measured from first treatment than the interval of 4-12 week in univariate analysis (HR 2.74, 95% CI 1.39-5.39) and multivariate analysis (HR 2.39, 95% CI 1.19-4.77) (data not shown).

5.5 DISCUSSION

The present study was a hospital clinic-based retrospective study evaluating the relationship between treatment delays and survival, adjusting for socioeconomic, clinical, and pathological factors among 553 women with metastatic breast cancer. Survival was measured from metastatic breast cancer diagnosis, and from first treatment to control for immortal time bias. To our knowledge, no study has examined the connection between delayed treatment interval and survival among patients diagnosed with metastatic breast cancer with survival measured in two ways: survival from metastasis and from first treatment.

The study found that treatment delays of > 12 week, compared to 4-12 week had a marginal negative effect on survival from first treatment. Our study finding validates previous studies [41, 43, 88], as summarized in a systemic review performed by Richards el

al.[85] Investigators reported that patients experiencing delays of ≥ 3 months (which is considered as 12 weeks) had lower 5-year survival than patients with shorter delay.[85]

Only few studies have measured survival after first treatment related to the impact of treatment delays.[39, 41, 89, 112] As with the current study, researchers found that longer delays in treatment affected negatively on survival from first treatment.[41, 89] This finding is important as it shows that the impact of treatment delays on survival was accounted for immortal time effect.[109-111]

In the current study, treatment delay interval was reclassified into 4 groups (≤ 4 week, 4-12 week, 12-24 week, and > 24 week) and examined for the difference in survival between patients with delays of 4-12 week and patients with delays of 12-24 week to keep lead time effect to a minimum.[85] Considering the median survival measured from first treatment among 539 patients as 41 months (164 weeks), 8 weeks (difference median week between 4-12 week and 12-24 week) could compensate for lead time effect. In agreement with other studies [41, 43, 85, 90], 12-24 week of delays compared to 4-12 week of delays, was found to be a significant factor on survival from first treatment in multivariate analysis (HR 2.39, 95% CI 1.19-4.77) (data not shown).

Adverse survival outcomes were significantly associated with history of hypertension, ER/PR negative status, HER2 negative status, increasing number of metastasis, and liver metastasis, corroborating previous literatures.[9, 17, 28, 64, 75, 79, 82] Longer delays in treatment were related to two or more metastatic sites, and brain metastasis in this study, suggesting that patients having multiple metastatic sites at diagnosis spent more time on pre treatment workup. Additionally, if patients received

local cranial radiation and/or surgery for brain metastasis, the systemic therapy may have been delayed.

This study had limitations. We did not consider specific treatment regimens in the analysis, as study population was heterogeneous with respect to treatment regimen. However, it is reasonable to assume that treatments were selected in accordance with acceptable criteria and were carried out by competent physicians at this university affiliated, National Cancer Institute (NCI) designated site.

The study did not include 114 patients because medical records were unavailable for the secondary review, which could induce the possible sources of selection bias. The exclusion of patients whose charts were not found from the analysis did not appear to make significantly different changes in study results in terms of analyses of age, race, number of metastatic sites, metastatic location, ER/PR status and HER2 status.

We did the sensitivity test using available data of variables prior to imputation procedure compared to complete data of corresponding variables which were imputed, and there was no apparent difference in the frequency distribution and in the univariate analysis.

Seventy percent of patients in our study started treatments within 4 weeks of diagnosis of metastatic breast cancer (Table 10). National Breast and Cervical Cancer Early Detection Program (1991-1995) reported similar distribution (78.2%) of 30 days interval to diagnosis of any breast cancer and initiation of treatment.[113]

In conclusion, this is the first study, to our knowledge, to analyze the association between delays in treatment and survival among patients with metastatic breast cancer. Moreover, this study controlled for immortal time bias by measuring survival from the

initiation of treatment. The study demonstrated that delay of over 12 week in receiving treatment for metastatic breast cancer results in adverse survival outcomes: delays of > 12 week compared to 4-12 week had a marginal negative effect on survival from first treatment; furthermore, patients with delays of 12-24 week had significantly worse survival from first treatment than those with delays of 4-12 week. Utilizing a large database reflective of current metastatic breast cancer treatment this study employed a uniform protocol for data collection and examined prognostic factors in a comprehensive fashion. Findings of this study suggest the usefulness of targeted efforts to ensure prompt treatment initiation in patients diagnosed with metastatic breast cancer. Additionally, our findings highlight the need for future research into factors influencing delays in treatment and better understanding of these associations may lead to interventions that can improve breast cancer outcomes.

5.6 REFERENCES

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5.7 TABLES AND FIGURES

Table 8. Characteristics of patients with metastatic breast cancer by the length of treatment delay (≤4 week, 4–12 week, >12 week), identified at two sites of the UPMC, UPCI Breast Cancer Program

	Treatment delay					
	≤4 week (n=390)		4–12 week (n=129)		>12 week (n=34)	
Variable*	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Age (range 26-88 years), Median**	54.0		54.0		65.5	
Median Household income (range $18,473-$85,102), Median	41367.0		41044.2		39843.2	
Race						
Non-Black	365	(70.6)	122	(23.6)	30	(5.8)
Black	25	(69.4)	7	(19.4)	4	(11.1)
Education						
≤High School	189	(70.0)	64	(23.7)	17	(6.3)
> High School	201	(71.0)	65	(23.0)	17	(6.0)
BMI						
<20 kg/m^2	16	(51.6)	13	(41.9)	2	(6.5)
20-24.9 kg/m^2	88	(74.6)	25	(21.2)	5	(4.2)
25-29.9 kg/m^2	172	(68.0)	65	(25.7)	16	(6.3)
≥30 kg/m^2	114	(75.5)	26	(17.2)	11	(7.3)
Menopausal status						
Pre menopause	99	(71.2)	35	(25.2)	5	(3.6)
Post menopause	291	(70.3)	94	(22.7)	29	(7.0)
History of hypertension						
No	224	(70.9)	77	(24.4)	15	(4.8)
Yes	166	(70.1)	52	(21.9)	19	(8.0)
Charlson comorbidity score						
0	318	(72.4)	94	(21.4)	27	(6.2)
1	9	(60.0)	5	(33.3)	1	(6.7)
2	20	(62.5)	12	(37.5)	0	(0.0)
3+	43	(64.1)	18	(26.9)	6	(9.0)
Charlson Comorbidity Condition						
Congestive heart failure						
No	384	(71.0)	124	(23.0)	32	(5.9)
Yes	6	(46.1)	5	(38.5)	2	(15.4)
Chronic pulmonary disease						
No	376	(70.9)	123	(23.2)	31	(5.9)
Yes	14	(60.9)	6	(26.1)	3	(13.0)

Table 8 (Continued)

			Treatment delay			
Variable*						
Mild liver disease						
No	376	(71.1)	121	(22.9)	32	(6.1)
Yes	14	(58.3)	8	(33.3)	2	(8.3)
Diabetes						
No	365	(70.7)	119	(23.1)	32	(6.2)
Yes	25	(67.6)	10	(27.0)	2	(5.4)
ER/PR status**						
ER/PR positive	309	(76.5)	83	(20.5)	12	(3.0)
ER/PR negative	81	(54.4)	46	(30.9)	22	(14.8)
HER2 status						
HER2 positive	138	(72.3)	44	(23.0)	9	(4.7)
HER2 negative	252	(69.6)	85	(23.5)	25	(6.9)
Number of metastatic sites**						
1	253	(74.4)	65	(19.1)	22	(6.5)
2+	137	(64.3)	64	(30.0)	12	(5.6)
Metastatic location						
Brain**						
No	375	(72.2)	116	(22.4)	28	(5.4)
Yes	15	(44.1)	13	(38.2)	6	(17.7)
Bone						
No	173	(67.8)	64	(25.1)	18	(7.1)
Yes	217	(72.8)	65	(21.8)	16	(5.4)
Liver						
No	300	(68.6)	106	(24.3)	31	(7.1)
Yes	90	(77.6)	23	(19.8)	3	(2.6)
Other**						
No	189	(77.1)	40	(16.3)	16	(6.5)
Yes	201	(65.3)	89	(28.9)	18	(5.8)

Abbreviation: BMI, body mass index; ER/PR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor-2.

* Variables with < 1% of frequency were excluded from analysis.

** $P < 0.05$.

Table 9. Univariate analysis of survival relative to metastatic breast cancer diagnosis in patients (n = 553) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Variable**	Patients No. (%)	Hazard ratio	95% CI	P-value
Age	553 (100)	1.01	1.00-1.02	0.004
Race				
Non-Black	517 (93.5)	1.00	referent	
Black	36 (6.5)	1.46	0.88-2.42	0.148
Education*				
≤ High School	270 (48.8)	1.00	referent	
> High School	283 (51.2)	0.79	0.63-1.00	0.0495
BMI*				0.022†
<20 kg/m^2	31 (5.6)	1.00	referent	
20-24.9 kg/m^2	118 (21.3)	1.70	0.96-3.02	0.069
25-29.9 kg/m^2	253 (45.8)	1.13	0.65-1.97	0.666
≥30 kg/m^2	151 (27.3)	1.46	0.83-2.58	0.191
Menopausal status*				
Pre menopause	139 (25.1)	1.00	referent	
Post menopause	414 (74.9)	1.14	0.87-1.49	0.337
History of hypertension*				
No	316 (57.1)	1.00	referent	
Yes	237 (42.9)	1.60	1.26-2.03	0.0001
Charlson comorbidity score	553 (100)	1.08	0.99-1.18	0.067
Congestive heart failure				
No	540 (97.6)	1.00	referent	
Yes	13 (2.4)	1.85	0.87-3.94	0.108
Chronic pulmonary disease				
No	530 (95.8)	1.00	referent	
Yes	23 (4.2)	1.28	0.76-2.16	0.347
Mild liver disease				
No	529 (95.7)	1.00	referent	
Yes	24 (4.3)	1.34	0.75-2.39	0.325
Diabetes				
No	516 (93.3)	1.00	referent	
Yes	37 (6.7)	1.33	0.83-2.12	0.233
ER/PR status				
ER/PR positive	404 (73.1)	1.00	referent	
ER/PR negative	149 (26.9)	1.50	1.17-1.93	0.002
HER2 status				
HER2 positive	191 (34.5)	1.00	referent	
HER2 negative	362 (65.5)	1.28	1.00-1.64	0.047

Table 9 (Continued)

Variable**	Patients No. (%)	Hazard ratio	95% CI	P-value
Number of metastatic sites	553 (100)	1.36	1.20-1.55	<0.0001
Metastatic location				
Brain				
No	519 (93.9)	1.00	referent	
Yes	34 (6.1)	1.71	1.12-2.62	0.014
Bone				
No	255 (46.1)	1.00	referent	
Yes	298 (53.9)	1.21	0.95-1.52	0.1117
Liver				
No	437 (79.0)	1.00	referent	
Yes	116 (21.0)	1.46	1.11-1.91	0.006
Other				
No	245 (44.3)	1.00	referent	
Yes	308 (55.7)	1.02	0.81-1.28	0.891

Abbreviation: 95% CI, 95% Confidence Interval; BMI, body mass index; ER/PR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor-2.

* Missing data were replaced with imputed data using simple imputation procedure of EM algorithm.[106]

** Variables with P value≈1.0 or with < 1% of frequency were excluded from analysis.

† P-value for omnibus test.

Table 10. Cox regression analysis between treatment delay (≤4 week, 4–12 week, >12 week) and survival from metastatic breast in patients (n = 553) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Survival measured from metastatic breast cancer diagnosis							
		Univariate analysis			Multivariate analysis¶		
Variable	**Patients No. (%)**	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
Treatment delay	553 (100.0)			0.194†			0.761†
≤4 week*	390 (70.5)	1.11	0.83-1.48	0.483	1.09	0.81-1.47	0.578
4–12 week**	129 (23.3)	1.00	referent		1.00	referent	
>12 week***	34 (6.2)	1.56	0.96-2.56	0.075	1.20	0.71-2.01	0.499

Abbreviation: 95% CI, 95% Confidence Interval.

¶ Cox regression was performed for examining the effect of treatment delay on survival, adjusted by covariates (BMI, history of hypertension, ER/PR status, HER2 status, number of metastatic sites, and liver metastasis), selected to be significant with P-value <0.05 by backward stepwise selection.

* Patients (n = 2) who were either censored or died within 4 weeks after metastatic diagnosis without receiving treatment were included in analysis.

** Patients (n = 4) who were either censored or died between 4 weeks and 12 weeks after metastatic diagnosis without receiving treatment were included in analysis.

*** Patients (n = 8) who were either censored or died more than 12 weeks after metastatic diagnosis without receiving treatment were included in analysis.

† P-value for omnibus test.

Table 11. Cox regression analysis between treatment delay (≤4 week, 4–12 week, >12 week) and survival from first treatment in patients* (n = 539) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Survival measured from first treatment							
		Univariate analysis			Multivariate analysis**		
Variable	**Patients No. (%)**	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
Treatment delay	539 (100.0)			0.037†			0.148†
≤4 week	388 (72.0)	1.10	0.82-1.47	0.537	1.05	0.78-1.43	0.741
4–12 week	125 (23.2)	1.00	referent		1.00	referent	
>12 week	26 (4.8)	2.02	1.16-3.54	0.014	1.76	0.99-3.13	0.056

Abbreviation: 95% CI, 95% Confidence Interval.

* Patients (n=14 among 553) who were either censored or died before first treatment were excluded from analysis.

** Cox regression was performed for examining the effect of treatment delay on survival, adjusted by covariates (BMI, history of hypertension, ER/PR status, HER2 status, number of metastatic sites, and liver metastasis), selected to be significant with P-value <0.05 by backward stepwise selection.

† P-value for omnibus test.

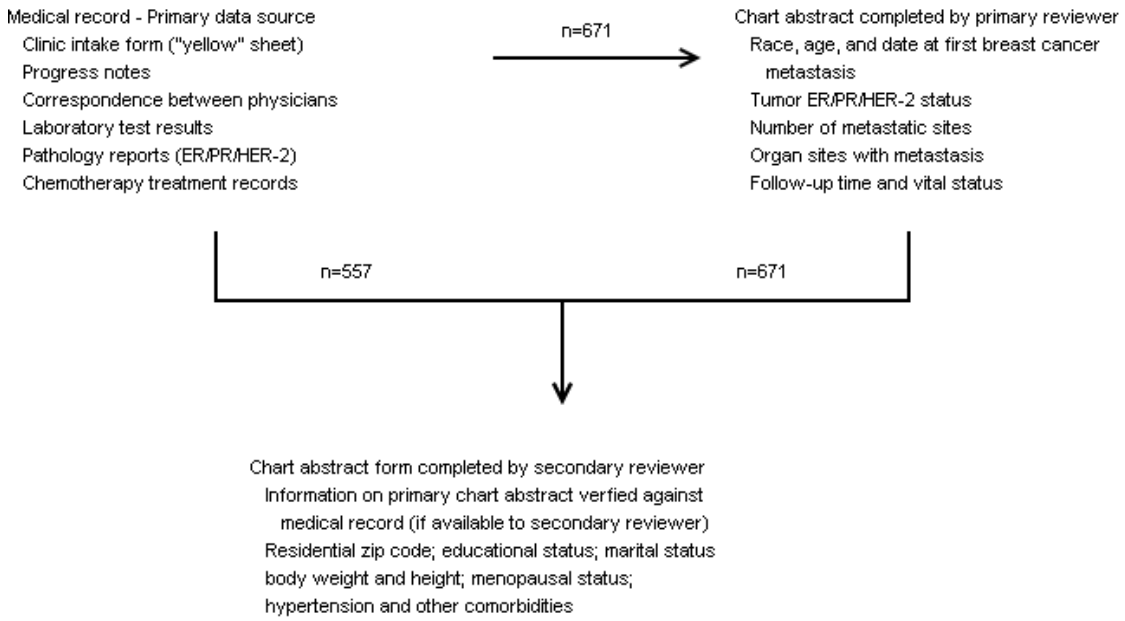

Figure 10. Medical record abstraction procedure

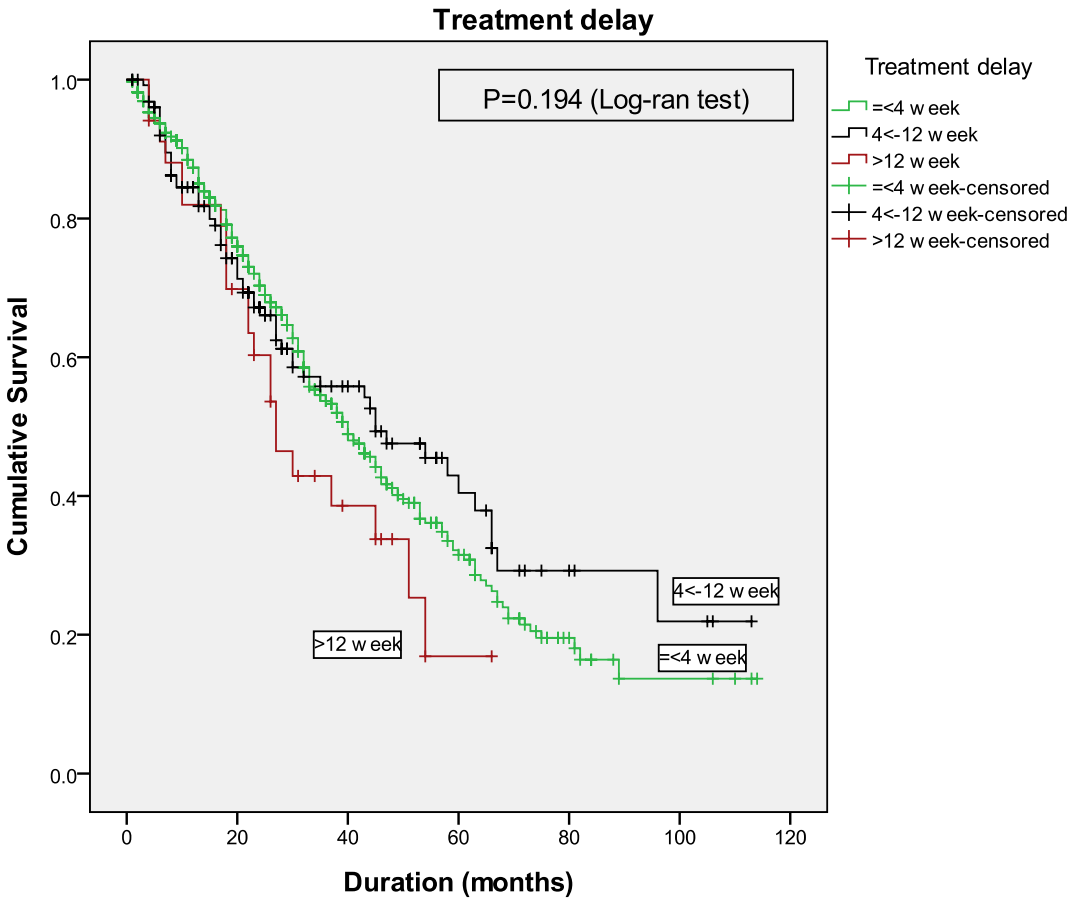

Figure 11. Kaplan-Meier's curve of survival since metastatic breast cancer diagnosis by treatment delay (≤4 week, 4–12 week, >12 week) in patients (n = 553) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

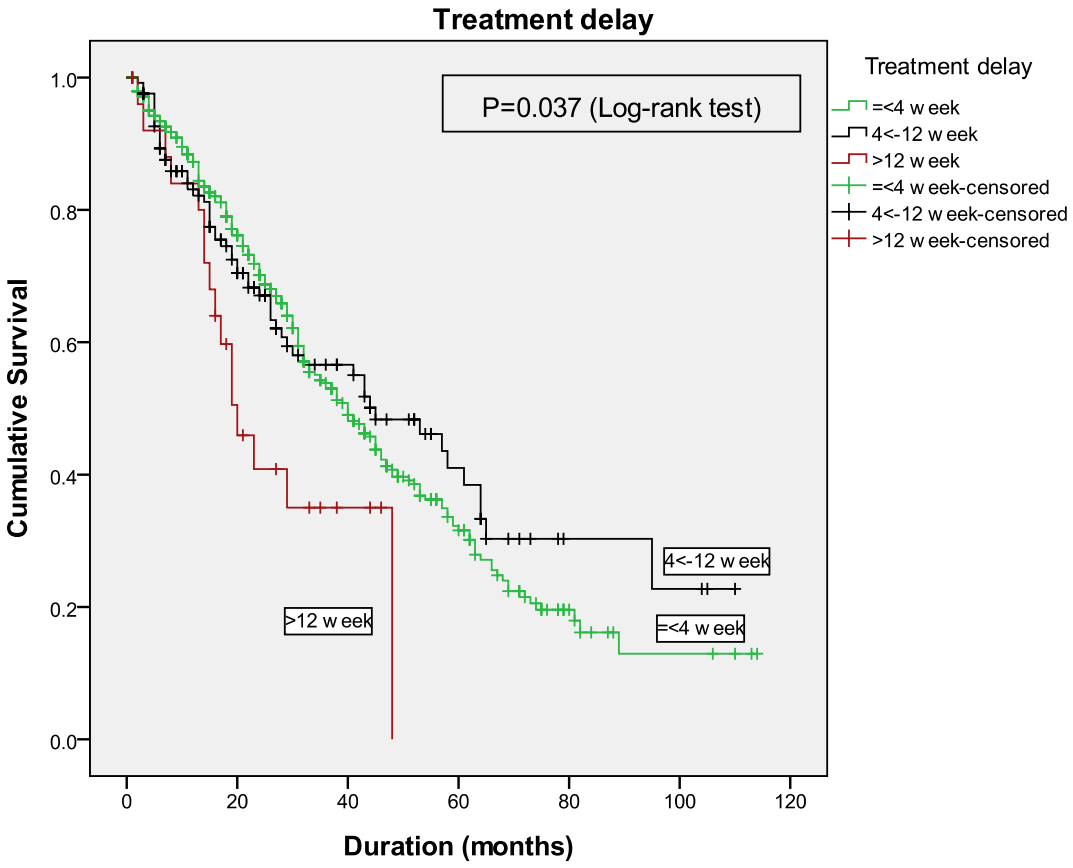

Figure 12. Kaplan-Meier's curve of survival since first treatment by treatment delay (≤4 week, 4–12 week, >12 week) in patients (n = 539) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

6.0 COMORBIDITY AS A POTENTIAL MEDIATOR OF SURVIVAL DISPARITY BETWEEN YOUNGER AND OLDER WOMEN DIAGNOSED WITH METASTATIC BREAST CANCER

To be submitted for publication

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Running Title: Comorbidity as a potential mediator

6.1 ABSTRACT

Background: The presence of comorbidity becomes increasingly important for its prognostic effect on survival in breast cancer patients with advancing age. The purpose of the present study was to evaluate the role of comorbidities including hypertension as a mediator of disparity in survival following metastasis between younger (≤ 51 years) and older (> 51 years) patients.

Populations and Methods: A total of 553 patients aged 26 to 88 years with the initial breast cancer metastasis diagnosis from one large urban practice have been followed up between January 1, 1999 and June 30, 2008. Comorbidity variables and outcomes of these patients were analyzed using Cox regression model. To assess comorbidity variables as a mediator of age-survival relationship, we applied two approaches: 1) Baron Kenny approach, and 2) alternative assessment to compute the percentage change in the HRs.

Results: The median survival was 40 months (range 1-114 months), with 265 (47.9%) alive and 288 (52.1%) dead at the end of the follow-up period. Older patients had worse survival than younger patients (HR 1.43, 95% CI 1.11-1.84) after adjustment of covariates. Hypertension was related to survival (HR 1.45, 95% CI 1.12-1.89) when age and other covariates were controlled. Hypertension augmented Charlson comorbidity score (hCCS) was a significant prognostic factor of survival (1 vs. 0 score, HR 1.40, 95% CI 1.07-1.83; 2 vs. 0 score, HR 1.88, 95% CI 1.22-2.89) in mutivariate analysis, explaining survival disparity between younger and older patients by 44% compared to 40 % of hypertension and 14% of the Charlson comorbidity score (CCS).

Conclusion: The study demonstrated that hypertension/hCCS was a prognostic factor for metastatic breast cancer survival. HCCS explained the age-survival relationship better than hypertension or CCS. Additionally, hypertension and hCCS were found to be strong mediators of the relationship between age and survival among patients with breast cancer metastasis. Findings of this study suggest that hypertension should be included in the comorbidity information for decision making support programs to aid patient consultation.

Key words: advanced breast cancer, comorbidity, hypertension, mediation

6.2 INTRODUCTION

Breast cancer is the most common cancer in women in the United States and in other industrialized countries, and the second leading cause of death for women with cancer.[110] Despite improved techniques for breast cancer screening, as many as 7% of women present with metastatic disease at the time of diagnosis.[101] While most women are diagnosed at an early stage, 20% to 80% of these patients, depending on the initial stage and the treatment strategy followed, will develop distant metastasis within five years of their initial diagnosis.[63]

Incidence rates of breast cancer increased with advancing age and this increase has occurred predominantly in women over 50 years.[44, 45] Mortality from breast cancer also increases with age.[8, 12, 44, 46-50] Large number of older women with breast cancer have coexistent diseases (comorbidities) at the time of diagnosis, which may influence their treatment options and survival.[26, 47, 49, 55, 56, 96]

Comorbidity at diagnosis can have an adverse impact on survival. Specially, Braithwaite et al reported that hypertension was related to survival since breast cancer diagnosis even after adjustment of age, race, and other covariates.[28] The presence of comorbid conditions and its treatment could place older patients at a greater risk of dying from breast cancer. Several studies examined the prediction of the comorbidity on survival in elderly breast cancer patients aged over 65 or 75 years [47, 48, 51-54], but the role of comorbidity as a mediator which accounts for relationship between age and survival has not been clearly documented.

While several comorbidity measurement systems exist, the Charlson comorbidity index (CCI) has been most popularly studied and considered to be a valid and reliable method of assessing comorbidity for cancer research.[58] Recent reports suggest that the CCI did not include certain comorbidities such as hypertension that did not contribute to a high relative risk in their study population.[48, 59] Hypertension is the most prevalent comorbidity among older breast cancer patients, and it affects mortality from breast cancer.[28, 47, 50, 53, 55, 56]

This study aimed to evaluate the role of comorbidities including hypertension as a mediator of disparity in survival following 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 U.S. undergo menopause at the mean age of 51 [114, 115], and women of > 51 years could be different from women of ≤ 51 years biologically, and clinically in term of the breast cancer influencing cancer treatment, and survival.[45, 116] 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 Charslon comorbidity score (hCCS) adding hypertension as a comorbid condition to the Charlson comorbid index, 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.

6.3 POPULATIONS AND METHOD

6.3.1 Patients Selection

The study included 553 patients with the first breast cancer metastasis seen at two urban hospitals (Montefiore and Magee) of the University of Pittsburgh Medical Center (UPMC) and by the University of Pittsburgh Cancer Institute (UPCI) Breast Cancer Program physicians. Patients with metastatic breast cancer were identified from daily hospital clinic lists and confirmed with medical records through clinical, radiological, or pathologic exams. Inclusion criteria included female patients aged eighteen 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 excluded because their medical records were unavailable for the secondary review. Additionally, 4 patients were excluded because they did not have history of clinic follow-up (i.e., missing information for treatment) prior to the first treatment or until study end point. This study was approved by the University of Pittsburgh Institutional Review Board.

6.3.2 Data Collection

The medical record abstraction protocol was developed (Figure 13). Retrospective review of medical records according to study protocol was utilized. 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.

Age, race, estrogen receptor (ER) and/or progesterone receptor (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 primary reviewer. Quality guaranteed protocol for the secondary chart review was established. The weighted kappa coefficients of secondary chart abstraction with n = 23, and of repeated chart abstraction with n = 23 for Charlson comorbidity score were 0.88 (95% CI 0.64-1.00) and 0.88 (95% CI 0.66-1.00), respectively; secondary and repeated chart abstraction for hypertension were 0.93 (95% CI 0.79-1.00) and 1.00 (95% CI 1.00-1.00), respectively.

Secondary chart retrieval procedure was performed to evaluate marital status, socioeconomic status (SES) including insurance, education, residential zip code, BMI at breast cancer diagnosis and at study entry, weight change (difference weight between at metastasis and weight at breast cancer diagnosis), 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 40% missing data such as marital status, insurance, BMI at breast cancer diagnosis and weight change were excluded for purposes of the analysis. Missing data imputation procedure was accomplished on education, median household income, BMI (at study entry), menopausal status and hypertension having missing values ranged 5% to 35% (hypertension 5%, menopause 11%, education 13%, BMI 20%, income 35%).

6.3.3 Predictor variables

Demographic or socioeconomic variables included age, race, education, median household income, BMI, and menopausal status. The median household income was linked to residential zip code matched to U.S. 2000 census summary file 3.[103] The BMI was calculated as a weight in kilogram (kg) divided by a height in meters squared and classified into four groups: less than 20kg/m^2 (underweight), 20-24.9kg/m^2 (normal), 25-29.9kg/m^2 (overweight), 30kg/m^2 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 used the pathologic report following the first metastatic site biopsy, if available, and the initial breast cancer site biopsy, otherwise. Metastatic locations were categorized into four 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 time in days between the date of initial breast cancer metastasis and the date of the initiation of first treatment. The date of first treatment initiation was considered as the date of the start of first treatment obtained from paper-version medical records. Treatment types included systematic therapy such as chemotherapy, hormonal therapy, immunologic therapy, vaccine therapy, and other biologic therapy. Treatment delay interval was categorized into 3 groups: less than or equal to 4 weeks, more than 4 weeks to less than or equal to 12 weeks, and more than 12 weeks.

Comorbidity variables included hypertension, Charlson comorbidity conditions, Charlson comorbidity score, and hypertension augmented Charlson comorbidity score. The comorbidity conditions were assessed from medical records at the time of metastasis including the previous history. Hypertension was defined as a blood pressure greater than or equal to 140 mmHg systolic pressure or greater than or equal to 90 mmHg diastolic pressure (American Heart Association) [104], at least twice presented at different visits. Hypertension included controlled hypertension. The Charlson comorbidity score (CCS), a composite of 19 comorbidity conditions was constructed using 18 comorbidity conditions (without metastatic solid tumor) which were weighted by 1 point for 10 conditions, 2 points for 6 conditions, 3 points for 1 condition and 6 points for 1 condition.[58, 105] 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.[105] The sum of the weighted comorbidity conditions has a theoretical range between 0 and 31. Charlson comorbidity score did not add the age-comorbidity combined risk score for the purposes of analyses. Hypertension-augmented Charlson comorbidity score (hCCS) was

constructed by assigning the weight of 1 point to hypertension and adding to the CCS (Table 12).[28] The difference between CCS and hCCS was that hCCS included hypertension by 1 point with CCS conditions.

6.3.4 Outcome variable

The outcome variable was an overall survival in months (defined as interval between metastatic breast cancer diagnosis and death or study end point). The study ascertained the occurrence of death in two ways. For in-hospital deaths, the hospital record was reviewed. For out of hospital deaths, the data were confirmed utilizing U.S. social security death index. Analyses censored all followed on June 30, 2008.

6.3.5 Statistical analysis

Simple imputation procedure for missing data used SPSS implementation of the Expectation Maximization (EM) algorithm of Dempster, Laird and Rubin (1977).[106] The frequency distribution of complete data of variables which were imputed was compared to the available data of corresponding variables prior to imputation using appropriate two sample t-tests for continuous variables and chi-squared statistics for categorical variables. Multicollinearity was assessed by using coefficient of multiple determination (R^2), tolerance, and variance-inflation factor (VIF) for each predictor variable using remaining covariates as its predictors.

Wilcoxon rank sum test and chi-squared statistics were used to identify statistically significant differences between younger and older group for continuous and

categorical variables, respectively. Log rank test was conducted to evaluate the relationship between predictor variables and survival. Kaplan-Meier estimation was used to generate survival curve for age variable. Odds ratios (ORs) and 95% confidence interval (95% CI) of younger vs. older group were obtained from binary logistic regression for hypertension, and ordinal logistic regression (assuming proportional odds) for CCS, and hCCS. 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 produce hazard ratios (HRs) and 95% confidence interval (95% CI). A similar modeling approach was also applied using accelerated, failure-time model assuming a Weibull error distribution.[107]

To assess the comorbidity variables (hypertension, CCS, and hCCS) as a mediator of age-survival relationship, we applied two approaches: 1) Baron Kenny approach [117-120], and 2) alternative assessment to compute the percentage change in the HRs.[59, 117, 120-126] The formal analysis to detect the 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, i.e., age in this study) significantly predicts Y (outcome of interest, i.e., survival in this study), 2) X significantly predicts M, 3) M significantly predicts Y controlling for X.[117-120] These criteria are assessed by estimating the following equations:

$$Y = \acute{\imath}_1 + cX \qquad (1)$$

$$M = \acute{\imath}_2 + aX \qquad (2)$$

$$Y = \acute{\imath}_3 + c'X + bM \qquad (3)$$

where ί is an intercept coefficient.[118, 119]

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 include all covariates and age with a model that include all covariates and age and comorbidity variables, and examine percentage changes in the HRs for the age-survival relationship. The percentage change in the HRs was computed as:

$((HR_{\text{without comorbidity}} - HR_{\text{comorbidity}}) / (HR_{\text{without comorbidity}}-1.0)) \text{ X } 100$

where $HR_{\text{comorbidity}}$ denotes the HR for the effect of age on survival after adjustment of comorbidity.[59, 117, 120-126]

Two tailed p-value of less than 0.05 was considered significant. SAS (version 9.2) and SPSS (version 17.0) were used.

6.4 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 265 (47.9%) women having survived and 288 (52.1%) having died. Of the 553 patients included in the analysis, the majority of patients were non-black (93.5%), post menopausal (74.9%), Charlson comorbidity condition-free (79.4%), ER/PR positive (73.1%), HER2 negative (65.5%), and had metastasis at only one site (61.5%). The median household income was $41,190 (range $18,473-$85,102) and 283 (51.2%) patients had more than high school education. Most patients (73.1%) were overweight (n = 253, 45.8%) or obese (n = 151, 27.3%), while other patients were of normal weight or underweight group (n = 149, 26.9%). The median treatment delay interval was 13 days

(25 percentile 0 day and 75 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 vs. > 51 years) are displayed in Table 13. The median age was 55 years (range 26-88 years) and 107 patients in the younger group (≤ 51 years) relative to 181 patients in older group (> 51 years) died. Patients of > 51 years were more likely to have lower income level (P = 0.0007), less than or equal to high school education (P < 0.0001), and present with post menopausal (P < 0.0001) and HER2 negative (P = 0.018) status compared to patients of ≤ 51 years. Hypertension (P < 0.0001) and more than or equal to one score of hCCS (P < 0.0001) were more likely to be found in older group.

6.4.1 *Univariate analysis*

Patients with metastatic breast cancer had significantly unfavorable outcomes when they were in the older group (P = 0.008) (Figure 14), having less than or equal to high school education (P = 0.0495), hypertension (P = 0.0001), one or two score of hCCS (0 vs. 1, P = 0.001; 0 vs. 2, P = 0.011), ER/PR negative (P = 0.002), and HER2 negative (P = 0.047). In addition, patients diagnosed with greater number of metastatic sites (P < 0.0001), brain metastasis (P = 0.014) or liver metastasis (P = 0.006) had significantly worse prognoses. The CCS (P = 0.067) for one unit increase and the normal body weight group (P = 0.069) compared to the underweight group had a marginal negative effect on survival (data not shown).

6.4.2 *Comorbidity variables (hypertension, CCS, and hCCS) and age*

Multivariate logistic regression was conducted for the relationship between age and three comorbidity variables (Table 14). Patients aged > 51 years were more than four times as likely as patients aged ≤ 51 years to have hypertension (OR 4.66, 95% CI 3.11-6.99). Older patients (> 51 years) had 2.58 times the odds of one or more CCS relative to zero CCS, two or more CCS relative to zero or one CCS, and three or more CCS relative to zero, one, or two CCS (OR 2.59, 95% CI 1.58-4.24) compared to younger patients (≤ 51 years); the odds of older patients was about four times higher to have hCCS (1+ vs. 0; 2+ vs. 0, 1; 3+ vs. 0, 1, 2) than younger patients (OR 3.94, 95% CI 2.73-5.69).

6.4.3 *Comorbidity variables and outcome of interest*

Table 15 showed 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 one or two score was associated with survival compared to the zero score of hCCS (1 vs. 0, HR 1.40, 95% CI 1.07-1.83; 2 vs. 0, HR 1.88, 95% CI 1.22-2.89). The 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 HER2 positive and in HER2 negative status was not modified by age group.

6.4.4 *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 comorbidity variables, 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 16). 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.[117, 118] When using accelerated failure-time models assuming a Weibull distribution [107], results were comparable to those in multivariate analysis using Cox regression models (data not shown). The menopausal status was excluded for adjustment in multivariate model because its collinearity with age on survival and it's standing in the causal pathway between age and survival, the association of age and survival can be underestimated.

6.5 DISCUSSION

The present study was a hospital clinic-based study evaluating the role of comorbidity as a mediator of survival disparity between younger and older group and comparing the

magnitudes to which each comorbidity variable (hypertension, CCS, and hCCS) mediated the age-survival relationship. To our knowledge, this is the first study to assess the role of comorbidity as a mediator between age and survival among metastatic breast cancer patients. Furthermore, we added hypertension as a comorbid condition to the Charlson comorbid index, creating hypertension augmented Charlson comorbidity score (hCCS) and compared the extent to which hCCS explained the poor survival of older than younger group, relative to other comorbidity variables (hypertension, and CCS).

The study found that hypertension/hCCS was a strong predictor of survival following breast cancer metastasis, and hCCS was better than CCS (14%) or hypertension alone (40%) to explain disparity between the younger and older group in survival by 44% after accounting for all covariates. Moreover, hypertension and hCCS were found to be a strong mediator because the effect of age on survival was not significant after adjustment of hypertension or hCCS (Table 16).[117, 118]

Consistently with previous studies [8, 12, 44, 49, 65], our study found that older age (> 51 years) had an adverse impact on survival than younger group (≤ 51 years). Specifically, Largillier et al reported that excess mortality rate increased with patients more than 50 years relative to patients of less than 50 years in stage IV breast cancer.[8] Several studies showed that younger patients had better survival than older patients [8, 12, 46-49], 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 comorbid conditions which place the older group at greater risk of poor prognosis on the course of metastatic disease.[46]

In agreement with previous studies [47, 48, 56, 96], the current study found that comorbid 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 comorbid condition among breast cancer patients [47, 48, 50, 53, 56, 96, 98], and was more likely to be found in older patient group.[56] Hypertension can potentially be an important risk factor for cancer morbidity and mortality. For example, cell death by apoptosis can influence the growth of vascular smooth muscle cells (VSMCs) and the increased proliferation of VSMCs responds exaggeratedly to growth stimuli, which is characterized by shortening of the cell cycle. This mechanism may lead to increased cellular proliferation.[57]

We observed an association between hypertension and survival after diagnosis of metastatic breast cancer even after adjustments of age and other covariates (Table 15), corroborating previous literature.[28]

Our chart abstraction procedure detected Charlson comorbidity in 21% of cases which is in concordance with other studies.[26, 49, 52, 95] In this study, we found that Charlson comorbidity score (CCS) for one unit increase had a marginal adverse effect on survival in univariate analysis, but was not significant after accounting for age and other covariates in consistent with another study.[47] Additionally, CCS by itself was not a strong mediator of age-survival relationship, however, hCCS, combining hypertension with CCS explained the survival disparity between younger and older age group by 44% relative to 14% of CCS and 40% of hypertension alone, indicating that hCCS was a better than CCS or hypertension to describe the age-survival relationship.

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, a hypertension.

This study had limitations. We did not consider specific treatment regimens in the analysis, as study population was heterogeneous with respect to treatment regimen. However, it is reasonable to assume that treatments were selected in accordance with acceptable criteria and were carried out by competent physicians at this university affiliated, National Cancer Institute (NCI) designated site.

The study did not include 114 patients because medical records were unavailable for the secondary review, which could induce the possible sources of selection bias. Exclusion of patients whose charts were not found from the analysis did not appear to make significantly different changes in study results in terms of analyses of age, race, number of metastatic sites, metastatic location, ER/PR status and HER2 status (data not shown).

We performed sensitivity test using available data of variables prior to imputation procedure compared to complete data of corresponding variables which were imputed, and there was no apparent difference in the frequency distribution and in the univariate analysis. In addition, our study findings were fairly robust since similar results using semi-parametric, Cox regression and parametric, accelerated failure-time models were obtained (data not shown).

Our data collection procedure extracted comorbidity information from multiple medical record sources (Figure 13), including clinic intake forms, progress notes,

laboratory results, and physician summaries. Medical record documentation was not strictly uniform over the period of time (January 1, 1999 through June 30, 2008) covering first diagnosis of metastatic breast cancer. For example, medical records for women with breast cancer metastasis diagnosed during an early time period were missing a clinic intake form more frequently than medical records for women diagnosed during a later time period (data not shown). This type of calendar time-related variability in medical record completeness or quality may have introduced a systemic error leading to 1) the underestimation of Charlson comorbidity during early time periods and 2) the failure to detect association between Charlson comorbidity and survival because of concurrent improvements in the effectiveness of medical treatment for metastatic breast cancer. In our study, however, Charlson comorbidity score values were independent of the year of first diagnosis of metastatic breast cancer (data not shown). Assuming similarly ill women were diagnosed with metastatic breast cancer in earlier and later time periods, this result suggests that variable medical record quality did not adversely affect our results associating the Charlson comorbidity measurements with survival.

In conclusion, this is the first study, to our knowledge, to assess the role of comorbidity as a mediator of the age-survival relationship among patients with metastatic breast cancer. Moreover, we created hCCS variable combining Charlson comorbidity score with hypertension and compared the extent to which survival difference between younger and older age group may be explained by hCCS relative to other comorbidity variables (hypertension, and CCS). The study demonstrated that hypertension/hCCS was a prognostic factor on survival following metastasis, and hCCS explained better than hypertension or CCS for age-survival relationship. Additionally, hypertension and hCCS

were found to be a strong mediator of the relationship between age and survival among patients with breast cancer metastasis.

Utilizing a large database reflective of current metastatic breast cancer treatment, this study employed 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 physicians should balance the benefit of anti-cancer treatment against current health condition and the possible decrease of quality of life that may occur during cancer treatment.

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6.7 TABLES AND FIGURES

Table 12. Comorbidity conditions utilized for the construction of CCS and hCCS at the UPMC, UPCI Breast Cancer Program

	Comorbidity conditions	Assigned weight
Charlson comorbidity condition [58]	Myocardial infarct	1
	Congestive heart failure	1
	Peripheral vascular disease	1
	Cerebrovascular disease	1
	Dementia	1
	Chronic pulmonary disease	1
	Connective tissue disease	1
	Ulcer disease	1
	Mild liver disease	1
	Diabetes	1
	Hemiplegia	2
	Moderate or severe renal disease	2
	Diabetes with end organ damage	2
	Any tumor	2
	Leukemia	2
	Lymphoma	2
	Moderate or severe liver disease	3
	AIDS	6
Non-Charlson comorbidity condition	Hypertension	1

Abbreviation: CCS, Charlson comorbidity score; hCCS, hypertension augmented Charlson comorbidity score.

Table 13. Characteristics of patients with metastatic breast cancer by age (≤51 years, >51 years), identified at two sites of the UPMC, UPCI Breast Cancer Program

	≤ 51 years (n = 223)		> 51 years (n = 330)	
Variable*	**No.**	**(%)**	**No.**	**(%)**
Median Household income (range $18,473-$85,102), Median**	$42,136.1		$40,680.3	
Race				
Non-Black	213	(41.2)	304	(58.8)
Black	10	(27.8)	26	(72.2)
Education**				
≤High School	81	(30.0)	189	(70.0)
> High School	142	(50.2)	141	(49.8)
BMI				
<20 kg/m^2	16	(51.6)	15	(48.4)
20-24.9 kg/m^2	57	(48.3)	61	(51.7)
25-29.9 kg/m^2	94	(37.2)	159	(62.8)
≥30 kg/m^2	56	(37.1)	95	(62.9)
Menopausal status**				
Pre menopause	134	(96.4)	5	(3.6)
Post menopause	89	(21.5)	325	(78.5)
ER/PR status				
ER/PR positive	159	(39.4)	245	(60.6)
ER/PR negative	64	(42.9)	85	(57.1)
HER2 status**				
HER2 positive	90	(47.1)	101	(52.9)
HER2 negative	133	(36.7)	229	(63.3)
Number of metastatic sites				
1	130	(38.2)	210	(61.8)
2+	93	(43.7)	120	(56.3)
Metastatic location				
Brain				
No	204	(39.3)	315	(60.7)
Yes	19	(55.9)	15	(44.1)
Bone				
No	102	(40.0)	153	(60.0)
Yes	121	(40.6)	177	(59.4)
Liver				
No	170	(38.9)	267	(61.1)
Yes	53	(45.7)	63	(54.3)

Table 13 (Continued)

	≤ 51 years (n = 223)		> 51 years (n = 330)	
Variable*	**No.**	**(%)**	**No.**	**(%)**
Other				
No	92	(37.5)	153	(62.5)
Yes	131	(42.5)	177	(57.5)
Charlson Comorbidity Condition				
Congestive heart failure**				
No	222	(41.1)	318	(58.9)
Yes	1	(7.7)	12	(92.3)
Chronic pulmonary disease				
No	217	(40.9)	313	(59.1)
Yes	6	(26.1)	17	(73.9)
Mild liver disease				
No	215	(40.6)	314	(59.4)
Yes	8	(33.3)	16	(66.7)
Diabetes**				
No	219	(42.4)	297	(57.6)
Yes	4	(10.8)	33	(89.2)
Treatment delay				
≤4 week	159	(40.8)	231	(59.2)
4–12 week	55	(42.6)	74	(57.4)
>12 week	9	(26.5)	25	(73.5)
CCS				
0	197	(44.9)	242	(55.1)
1	18	(22.5)	62	(77.5)
2	7	(24.1)	22	(75.9)
3+	1	(20.0)	4	(80.0)
hCCS**				
0	155	(56.8)	118	(43.2)
1	58	(29.3)	140	(70.7)
2	7	(12.1)	51	(87.9)
3+	3	(12.5)	21	(87.5)
Hypertension**				
No	176	(55.7)	140	(44.3)
Yes	47	(19.8)	190	(80.2)

Abbreviation: BMI, body mass index; ER/PR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor-2; CCS, Charlson comorbidity score; hCCS, hypertension augmented Charlson comorbidity score.

* Variables with < 1% of frequency were excluded from analysis.

** $P < 0.05$.

Table 14. Logistic regression odds ratios of age (≤51years vs. >51 years) predicting comorbidity variables (hypertension, CCS, and hCCS) among patients with metastatic breast cancer, identified at two sites of the UPMC, UPCI Breast Cancer Program

Outcome variable	≤51 years (n = 223)		>51 years (n = 330)		
	Odds ratio	95% CI	Odds ratio†	95% CI	P-value
Hypertension*	1.00	referent	4.66	3.11-6.99	<0.0001
CCS**	1.00	referent	2.59	1.58-4.24	0.0002
hCCS***	1.00	referent	3.94	2.73-5.69	<0.0001

Abbreviation: 95% CI, 95% Confidence Interval; CCS, Charlson comorbidity score; hCCS, hypertension augmented Charlson comorbidity score.

† Multivariate regression was adjusted by covariates (race, education, treatment delay, ER/PR status, HER2 status, number of metastatic sites, brain, bone, and liver metastasis); further adjustment including BMI did not significantly change the estimates.

* Hypertension was dichotomous (no vs. yes) as an outcome variable.

** CCS (0 vs. 1 vs. 2 vs. 3+) was analyzed as an outcome variable using ordinal logistic regression.

*** hCCS (0 vs. 1 vs. 2 vs. 3+) was analyzed as an outcome variable using ordinal logistic regression.

Table 15. Cox regression analysis between comorbidity (hypertension, CCS, and hCCS) and survival among patients with metastatic breast cancer, identified at two sites of the UPMC, UPCI Breast Cancer Program

Variable	No. (%)	Hazard ratio*	95% CI	P-value
Hypertension				
No	316 (57.1)	1.00	referent	
Yes	237 (42.9)	1.45	1.12-1.89	0.005
CCS				0.283†
0	439 (79.4)	1.00	referent	
1	80 (14.5)	1.35	0.96-1.91	0.088
2	29 (5.2)	1.34	0.80-2.25	0.266
3+	5 (0.9)	0.88	0.21-3.66	0.862
hCCS				0.013†
0	273 (49.4)	1.00	referent	
1	198 (35.8)	1.40	1.07-1.83	0.015
2	58 (10.5)	1.88	1.22-2.89	0.004
3+	24 (4.3)	1.42	0.78-2.56	0.248

Abbreviation: 95% CI, 95% Confidence Interval; CCS, Charlson comorbidity score; hCCS, hypertension augmented Charlson comorbidity score.

* Multivariate regression was adjusted by age and other covariates (race, education, treatment delay, ER/PR status, HER2 status, number of metastatic sites, brain, bone, and liver metastasis); further adjustment including BMI did not significantly change the estimates.

† P-value for omnibus test.

Table 16. Comorbidity (hypertension, CCS, and hCCS) as a mediator of the relationship between age and survival among patients with metastatic breast cancer, identified at two sites of the UPMC, UPCI Breast Cancer Program

Variable	Hazard ratio	95% CI	P-value
Hypertension			
Hazard ratio for age on survival adjusted by covariates*	1.43	1.11-1.84	0.005
Hazard ratio for age on survival adjusted by hypertension and covariates*	1.26	0.97-1.65	0.086
Proportion explained by hypertension for the effect of age on survival	40%		
CCS			
Hazard ratio for age on survival adjusted by covariates*	1.43	1.11-1.84	0.005
Hazard ratio for age on survival adjusted by CCS and covariates*	1.37	1.06-1.77	0.016
Proportion explained by CCS for the effect of age on survival	14%		
hCCS			
Hazard ratio for age on survival adjusted by covariates*	1.43	1.11-1.84	0.005
Hazard ratio for age on survival adjusted by hCCS and covariates*	1.24	0.95-1.63	0.110
Proportion explained by hCCS for the effect of age on survival	44%		

Abbreviation: 95% CI, 95% Confidence Interval; CCS, Charlson comorbidity score; hCCS, hypertension augmented Charlson comorbidity score.

* Multivariate regression was adjusted by covariates (race, education, treatment delay, ER/PR status, HER2 status, number of metastatic sites, brain, bone, and liver metastasis); further adjustment including BMI did not significantly change the estimates.

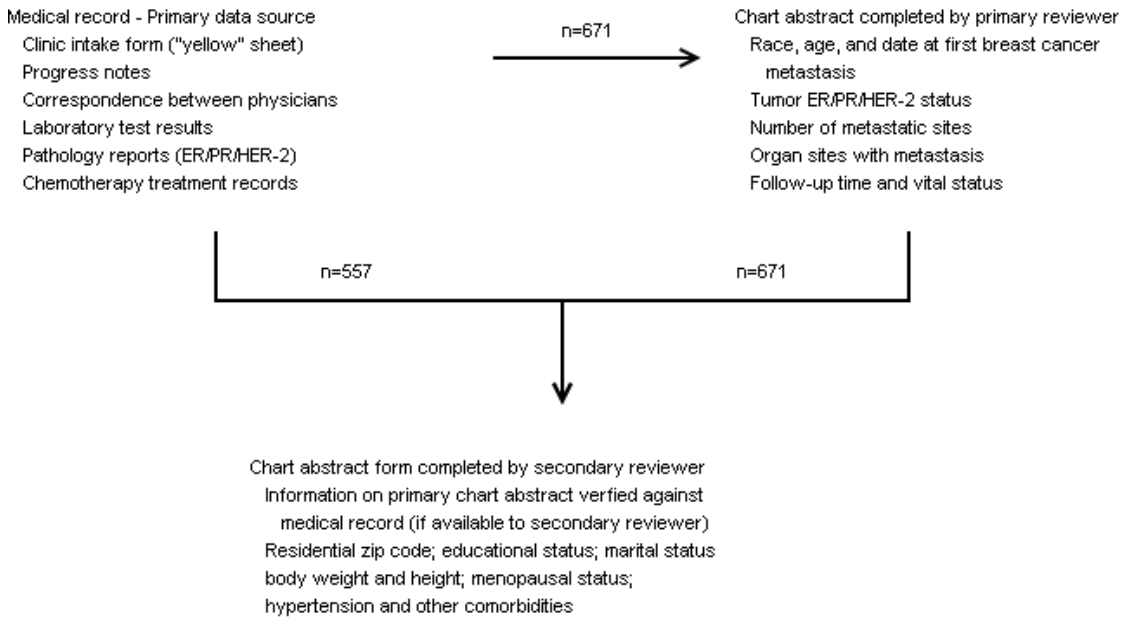

Figure 13. Medical record abstraction procedure

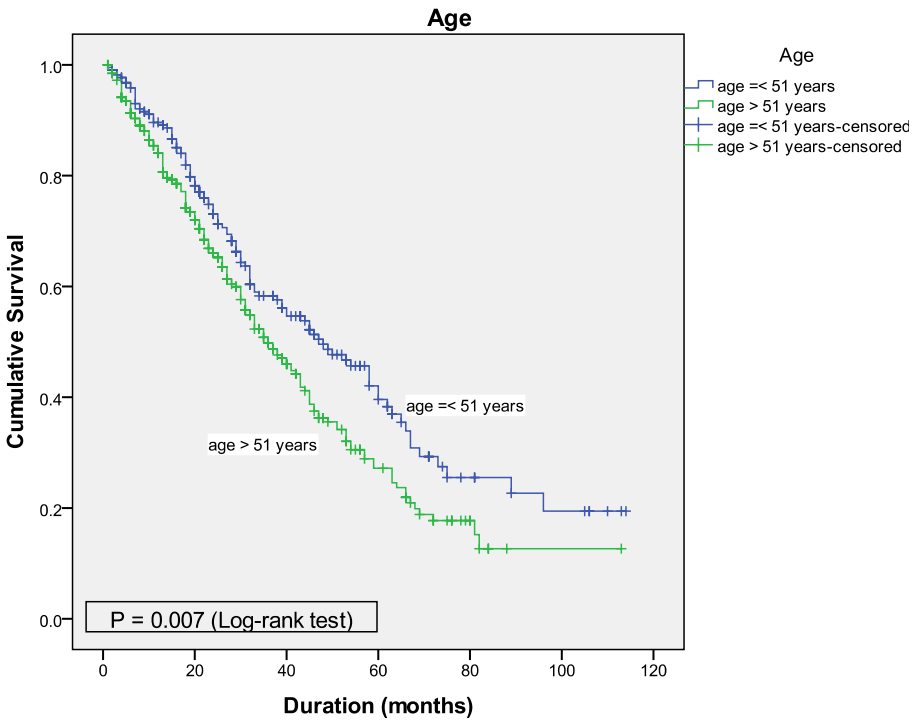

Figure 14. Kaplan-Meier's curve of survival by age in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

7.0 GENERAL DISCUSSION

Breast cancer is the most common cancer and the second leading cause of cancer mortality in women in the United States.[1] Distant metastasis of breast cancer is found among 7% of women with initial breast cancer diagnosis. Most of these women have poor survival outcomes.[7, 101]

Metastatic breast cancer patients represent a heterogeneous population with a varied clinical course, and different clinical outcomes underline the need for accurate prediction of survival based on prognostic factors. Many studies have considered individual risk factors, one at a time, but few studies have considered a comprehensive range of risk factors collectively.

Delay in receiving treatment for breast cancer may result in adverse prognostic outcomes among breast cancer patients. Epidemiologic studies examining the effect of treatment delay on survival after breast cancer diagnosis have yielded inconsistent results. For example, Gorin et al conducted a population based study with SEER database enrolling Medicare recipients 65 years and older women in breast cancer. Investigators observed that a delay of more than three months had less favorable outcomes than less than or equal to three months.[33] This contrasts with the findings of Charlson et al who investigated a hospital based retrospective study using 685 women diagnosed with breast cancer at Yale-New Haven Hospital, demonstrating that there were no significant

differences in survival with treatment delay less than three months vs. 3-6 months vs. more than six months of delays.[39]

The 5-year relative survival rate is remarkably higher among women diagnosed with breast cancer before age 50 compared to women diagnosed at ages 50 and older.[44] The higher prevalence of comorbid conditions in older women may influence their treatment options and survival [26, 47, 49, 55, 56, 96], but the role of comorbidity as a mediator which may explain the poorer survival in older women than younger women has not been clearly documented.

This study was designed to undertake the investigation of factors influencing survival following metastastic breast cancer diagnosis, to examine relationship between treatment delay and survival, and to evaluate the role of comorbidity as a mediator of age-survival relationship in women with metastatic breast cancer.

In this study, we investigated the effect of predictor variables on survival from the time of diagnosis of metastatic breast cancer: outcome of interest was overall survival (i.e., all causes of death). There is a need to analyze the effect of predictor variables on specific outcomes of interest by measuring breast cancer specific survival or evaluating competing cause survival (non-breast cancer cause) as an outcome of interest, and by assessing quality of life as an outcome variable.

In study aim 3, we applied Baron-Kenny approach to assess the role of comorbidity as a mediator of age-survival relationship. Baron-Kenny approach is considered a traditional method to evaluate mediation between indicator and outcome of interest, but this approach tends to miss a true mediation effect (Type II error), or lead to erroneously present mediation effect (Type I error) suffering from low statistical

power.[120] One of the statistically rigorous methods by which mediation hypotheses may be assessed is bootstrapping method which provides a direct significant test of the mediation effect.[127, 128] The bootstrapping approach (i.e., bootstrapping the sampling distribution of indirect effect) derives a confidence interval with effect size estimation of mediation effect in a wide variety of situations. This method does not require many assumptions as other tests, which is likely to make test findings more accurate than traditional mediation analysis. [119, 120]

Additionally, we evaluated comorbidity at the time of diagnosis of metastasis to assess this effect on survival following metastatic breast cancer, and to investigate this effect as a mediator between age and survival. More studies are needed to fully understand these associations by measuring comorbidity variables as time-varying covariates (i.e., comorbidity acquired after metastasis). We used comorbidity variable with the summary measures (i.e., Charlson comorbidity score) in the study analysis to assess this variable as a mediator of age-survival relationship; evaluating individual comorbid conditions such as diabetes, CHF, and CVD in the causal pathway between age and survival could extend knowledge explaining the different clinic outcomes between younger and older women with metastatic breast cancer, focusing on the role of specific co-morbid conditions.

7.1 ARTICLE 1: FACTORS ASSOCIATED WITH MORTALITY AFTER BREAST CANCER METASTASIS

In the study, we used a hospital clinic-based study evaluating factors such as demographic or socioeconomic, clinical, and pathological factors related to survival following metastatic breast cancer diagnosis among 557 women. We found that most relevant factors on survival were ER or PR status (HR 1.84, 95% CI 1.40-2.41), HER2 status (HR 1.45, 95% CI 1.09-1.93), hypertension (HR 1.53, 95% CI 1.14-2.07), and number of metastatic sites (HR 1.27, 95% CI 1.01-1.59). Our findings are similar to the previous study results reporting that ER or PR negative, HER2 negative had worse impact on survival, and demonstrating the significant associations between hypertension, or more than one organ site affected by metastasis, and survival. [7-11, 64, 75-81, 84 28] In contrast with other published reports [24-30], our study did not observe a significant association between comorbidity and survival. The comparability of our study result with other studies is limited due to the methodological limitation in our study: the variability in medical record completeness (i.e., lack of clinic intake form). Even though more medical records in women diagnosed in early time period lacked the clinic intake form than those in women diagnosed during a later time period, Charlson comorbidity score was independent of the year of diagnosis of metastasis, indicating that the variable medical record quality did not affect negatively our study results related to the assessment of Charlson comorbidity score with survival.

7.2 ARTICLE 2: THE EFFECT OF DELAYS IN TREATMENT FOR BREAST CANCER METASTASIS ON SURVIVAL

In this study, we measured survival in two ways: interval between metastatic breast cancer diagnosis and death or study end point, and interval from the date of the first treatment to the date of death or the end of follow-up period. We assessed the relationship between treatment delay and survival measured after diagnosis of metastasis of breast cancer, and after first treatment. We eliminated immortal time effect by measuring observation time on date of first treatment and reduced lead time bias by excluding women with very long treatment (>24 weeks) delay from the group of women exposed to treatment delay (>12 weeks). This exclusion may limit, but not completely eliminate, lead time bias as a source of concern. Before making strong etiologic conclusions about the effects of treatment delay on metastatic breast cancer outcomes, we looked for a consistent pattern of association, across all these analyses.

We found that delays more than 12 weeks in receiving treatment for metastatic breast cancer resulted in adverse survival outcomes after first treatment: compared to 4-12 weeks, delays of > 12 weeks had a negative effect on survival and furthermore, patients with delays of 12-24 weeks had worse survival than those with delays of 4-12 weeks. This study provided the first results of exploring the relationship between delays in treatment and survival among metastatic breast cancer patients by accounting for metastatic locations and number of organ sites affected by metastasis.

7.3 ARTICLE 3: COMORBIDITY AS A POTENTIAL MEDIATOR OF SURVIVAL DISPARITY BETWEEN YOUNGER AND OLDER WOMEN DIAGNOSED WITH METASTATIC BREAST CANCER

In this study, we assessed the role of each comorbidity variable including hypertension, Charlson comorbidity score (CCS), and hypertension augmented Charlson comorbidity score (hCCS) as a mediator which may explain survival difference (disparity) between older and younger women with metastatic breast cancer. To evaluate the comorbidity as a mediator of the age-survival relationship, we employed two approaches: 1) Baron Kenny approach and 2) alternative assessment to measure the amount to which comorbidity explains the age-survival relationship by computing the percentage change in the hazard ratios (i.e, indirect effect of comorbidity variable among total effect of age on survival, (c-c')/c). The computation of the result ((c-c')/c) using Cox regression model was comparable to the computation of the result using accelerated, failure-time model.

The study demonstrated 1) older patients had worse survival than younger patients, 2) hypertension or hCCS was related to survival since metastasis, and 3) hCCS explained the poorer survival of older than younger women by 44%, compared to 40% of hypertension, and 14% of CCS. Furthermore, hypertension and hCCS were found to be strong mediators between age and survival following metastasis.

As of December 2010, Charlson list of comorbidities does not include hypertension. The study findings suggest that future studies of clinical predictors of survival after metastatic breast cancer diagnosis should not rely only on Charlson comorbidities, but also include, at minimum, a history of hypertension.

7.4 STUDY STRENGTHS

We utilized a large clinical database reflecting current metastatic breast cancer treatment and treatment patterns for metastasis for up to ten years of follow-up. We employed a uniform protocol for data collection, and defined two brand new exposure variables such as treatment delay, and co-morbidity including individual and summary measures. We evaluated prognostic factors from several domains, including demographic, clinical, and pathological factors.

7.5 STUDY LIMITATIONS

This study had several limitations. We excluded 114 patients without available paper version medical records for the secondary review. Given that excluded patients had lower survival than patients included in the study analysis, the possible source of selection bias could not be excluded even though the analyses of age, race, number of metastatic sites, metastatic location, ER or PR status, and HER2 status on survival were not different between excluded and remaining patients in the study.

The calendar time-related variability in medical record completeness, resulting in missing data ranged up to 35% may have introduced a systemic error to our study findings. However, we did sensitivity test by using available data of variables before imputation procedure compared to complete data of corresponding variables after imputation, and there was no significant difference in the frequency distribution and in the results of the univariate analyses. Moreover, we obtained the similar results using

Cox regression and accelerated, failure-time models, indicating that our study findings are fairly robust.

8.0 PUBLIC HEALTH SIGNIFICANCE

Despite impressive advances of breast cancer treatment strategies, treatment of metastatic breast cancer remains palliative. Overall, metastatic breast cancer is a medical outcome associated with progressive life limiting illness. However, it is possible to distinguish between groups of women with outcomes better and worse than average, based on patients' comorbidities and other prognostic factors. This knowledge creates opportunity to tailor treatment approaches according to prognosis.

We found that hypertension at the time of metastatic breast cancer had an adverse impact on survival. Discovering the biologic explanation for the association between hypertension and adverse prognosis might provide new prevention or treatment opportunities.

Women who began systemic treatment late (i.e., more than 12 weeks after diagnosis of metastatic breast cancer) experienced reduced survival compared to women who began treatment early (i.e., 12 or fewer weeks after diagnosis of metastasis). Improved treatment outcomes may be achieved by efforts designed to avoid unnecessary delays in starting systematic treatment. Additionally, our study findings emphasize the need for future study to examine factors related to treatment delays and better understanding of these associations may induce the improvement of treatment outcomes.

In addition, older women experience worse survival than younger women. A higher prevalence of co-morbid illness may explain a substantial portion of this poor survival outcome in older women. Efforts that aim to manage co-morbid illness in older women may reduce the survival difference between older and younger women.

Finally, these study findings may form a foundation for the growing corpus of knowledge explaining the differences in treatment outcomes among patients diagnosed metastatic breast cancer, helping to support clinical initiatives that provide emotional and physical support for patients in order to ensure appropriate and timely treatment for metastatic breast cancer.

APPENDIX A

SUPPLEMENTAL TABLES AND FIGURES FOR SPECIFIC AIM 1

A.1 SAMPLE SIZE AND POWER ESTIMATION

We estimated the power by using the formula for the Cox regression model established by Hsieh, F.Y. et al and Schoenfeld D.A.[129, 130]

The 663 sample size and 0.6 event rate were used to calculate the power of evaluating factors related to mortality after breast cancer metastasis based on the MBC Study followed till June 30, 2008.

The power for racial disparity (i.e., black vs. non-black) in mortality after breast cancer metastasis was assessed by using 0.25 as a standard deviation (STD) of race, 0.0029 as a correlation coefficient (R-squared) of race with covariates, and several hazards ratios (HRs) ranged from 1.44 to 2.0 based on the upper 95% Confidence Interval (95% CI) according to the database of the MBC Study from January 1, 1999 to June 30, 2008 (Table 17).

The power for assessing the relationship between age as either continuous or binary (>= 55, < 55) variable and mortality outcome, was calculated from 0.5 as a STD of

age, 0.008 as a R-squared of age with covariates, and several HRs between 1.23 and 1.5 according to the upper 95% CI based on the MBC data base (Table 18).

We assessed the power for evaluating the association between ER/PR status (positive vs. non-positive) and mortality after breast cancer metastasis by choosing 0.46 as a STD of ER/PR status, 0.0054 as a R-squared of ER/PR status with covariates, and several HRs ranged from 1.3 to 1.74 using the upper 95% CI (Table 19).

The power of examining the relationship between HER2 status (positive vs. non-positive) and mortality outcome was calculated with 0.48 as a STD of HER2 status, 0.0558 as a R-squared of HER2 status with covariates, and several HRs (1.226 to 1.5) based on the upper 95% CI (Table 20). All calculations were conducted with the PASS software (NCSS, Kaysville, Utah) with a two sided test, 0.05 Type I error.

Table 17. Power calculation for racial disparity (i.e., black vs. non-black) related mortality after breast cancer metastasis

HR	Power
1.44	43.3 %
1.7	75.2 %
1.9	89.2 %
2.0	93.2 %

Type 1 Error = 0.05

Event rate = 0.6, R-squared = 0.0029, STD = 0.25

Sample size = 663 (Black=43, Non-Black=620)

Table 18. Power calculation for relationship between age (continuous or binary (>= 55, < 55) variable) and mortality

HR	Power
1.23	54.6 %
1.3	74.1 %
1.4	91.6 %
1.5	98.1 %

Type 1 Error = 0.05

Event rate = 0.6, R-squared = 0.008, STD = 0.5

Sample size = 663 (Black=43, Non-Black=620)

Table 19. Power calculation for association between ER/PR status (positive vs. non-positive) and mortality after breast cancer metastasis

HR	Power
1.3	67.0 %
1.4	86.8 %
1.74	99.9 %

Type 1 Error = 0.05

Event rate = 0.6, R-squared = 0.0054, STD = 0.46

Sample size = 663 (Black=43, Non-Black=620)

Table 20. Power calculation of relationship between HER2 status (positive vs. non-positive) and mortality

HR	Power
1.226	47.4 %
1.4	87.9 %
1.5	96.5 %

Type 1 Error = 0.05

Event rate = 0.6, R-squared = 0.0558, STD = 0.48

Sample size = 663 (Black=43, Non-Black=620)

A.2 SELECTION OF STUDY POPULATION

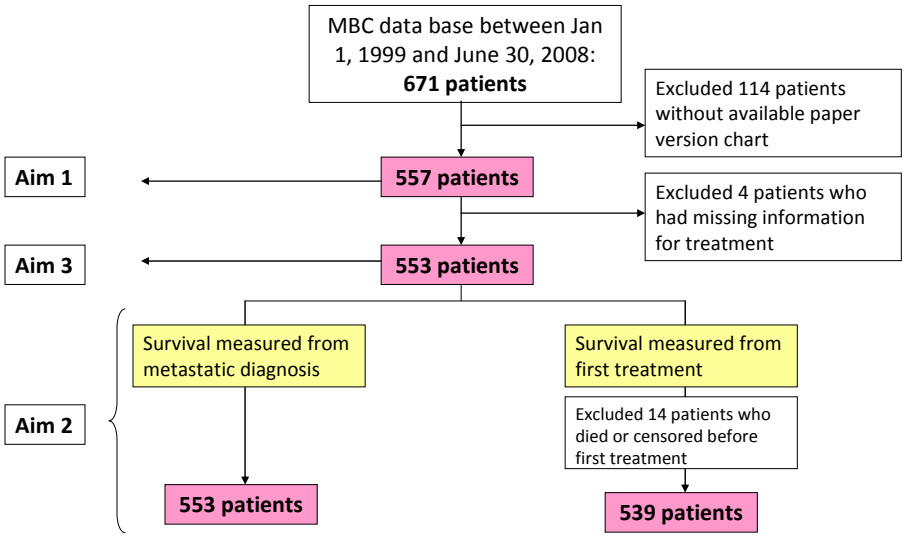

Figure 15. Selections of study population for each aim

A.3 MULTICOLLINEARITY

Table 21. Assessment of multicollinearity for each independent variable using remaining covariates as its predictors

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	.855	.172		4.974	.000		
	ImpIncome	4.712E-6	.000	.111	2.577	.010	.912	1.096
	M1M4	-.015	.197	-.004	-.076	.940	.545	1.836
	CHF	.047	.147	.015	.322	.747	.751	1.331
	DiabetesMild	-.005	.097	-.003	-.055	.956	.631	1.585
	LiverMild	.130	.104	.057	1.253	.211	.831	1.204
	COPD	-.028	.108	-.012	-.260	.795	.800	1.249
	M1M2M7	.141	.233	.031	.606	.545	.642	1.557
	ImpHer2	-.028	.043	-.028	-.641	.522	.883	1.133
	Liver	.016	.065	.014	.245	.806	.534	1.873
	Bone	-.021	.061	-.023	-.350	.727	.396	2.527
	Brain	-.011	.110	-.006	-.104	.917	.536	1.867
	ImpER	-.031	.046	-.029	-.671	.502	.908	1.102
	MetSite	-.008	.037	-.015	-.210	.834	.348	2.876
	Cimpcat4stageIIBMI	-.060	.046	-.057	-1.323	.186	.907	1.102
	Black	.113	.085	.059	1.334	.183	.851	1.176
	age	-.005	.002	-.141	-2.321	.021	.458	2.185
	ImpCharlson_Index	.000	.022	-.002	-.035	.972	.385	2.595
	ImpHypertension	-.117	.046	-.122	-2.541	.011	.737	1.357
	Other (Other, Adreanal, Lymphnode, Lung, Softtissue)	-.068	.070	-.072	-.977	.329	.309	3.237
	Impmeno	-.033	.057	-.031	-.579	.563	.600	1.666

a. Dependent Variable: ImpGths

Pearson Correlation Coefficient assessment of collinearity for Charlson comorbidity score and four Charlson comorbidity

```
proc corr data=collinearity;var impcharlson_index chf copd
livermild diabetesmild;run;
```

The CORR Procedure

5 Variables: ImpCharlson_Index CHF COPD LiverMild DiabetesMild

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ImpCharlson_Index	557	0.63555	1.41740	354.00000	0	7.00000
CHF	557	0.02334	0.15111	13.00000	0	1.00000
COPD	557	0.04129	0.19915	23.00000	0	1.00000
LiverMild	557	0.04309	0.20324	24.00000	0	1.00000
DiabetesMild	557	0.06643	0.24925	37.00000	0	1.00000

Simple Statistics

Variable	Label
ImpCharlson_Index	
CHF	CHF
COPD	COPD
LiverMild	LiverMild
DiabetesMild	DiabetesMild

Pearson Correlation Coefficients, N = 557
Prob > |r| under H0: Rho=0

	Imp Charlson_ Index	CHF	COPD	Liver Mild	Diabetes Mild
ImpCharlson_Index	1.00000	0.42605	0.34651	0.25440	0.53192
		<.0001	<.0001	<.0001	<.0001
CHF	0.42605	1.00000	0.08745	-0.03280	0.14977
CHF	<.0001		0.0391	0.4397	0.0004
COPD	0.34651	0.08745	1.00000	0.08927	0.01711
COPD	<.0001	0.0391		0.0352	0.6870
LiverMild	0.25440	-0.03280	0.08927	1.00000	0.01441
LiverMild	<.0001	0.4397	0.0352		0.7344
DiabetesMild	0.53192	0.14977	0.01711	0.01441	1.00000
DiabetesMild	<.0001	0.0004	0.6870	0.7344	

Assessment of collinearity for Charlson comorbidity score using four Charlson comorbidity conditions as its predictors

```
proc reg;model impcharlson_index=chf copd livermild
diabetesmild;run;
```

The REG Procedure

Model: MODEL1
Dependent Variable: ImpCharlson_Index

Number of Observations Read	671
Number of Observations Used	557
Number of Observations with Missing Values	114

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	619.47657	154.86914	171.82	<.0001
Error	552	497.53959	0.90134		
Corrected Total	556	1117.01616			

Root MSE	0.94939	R-Square	0.5546
Dependent Mean	0.63555	Adj R-Sq	0.5514
Coeff Var	149.38129		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	0.22826	0.04333	5.27	<.0001
CHF	CHF	1	3.16699	0.27073	11.70	<.0001
COPD	COPD	1	2.05052	0.20383	10.06	<.0001
LiverMild	LiverMild	1	1.62458	0.19911	8.16	<.0001
DiabetesMild	DiabetesMild	1	2.69017	0.16341	16.46	<.0001

A.4 CHARLSON COMORBIDITY CONDITIONS

Table 22. Frequency and Cox regression analysis for Charlson comorbidity conditions

	Frequency (%)	Univariate_HRs (P-value)	Multivariate_HRs (P-value)
MI	6 / 557 (1.1)	1.15 (.78)	1.18 (.75)
CHF	13 / 557 (2.3)	1.86 (.10)	1.67 (.22)
PVD	2 / 557 (0.4)	0 .00 (.97)	0.00 (.98)
CVD	8 / 557 (1.4)	1.30 (.65)	1.56 (.46)
Dementia	1 / 557 (0.2)	0.00 (.98)	0.00 (.985)
COPD	23 / 557 (4.1)	1.30 (.32)	1.29 (.35)
Connectivetissue	4 / 557 (0.7)	1.84 (.39)	1.69 (.47)
Ulcer	4 / 557 (0.7)	1.00 (1.00)	0.88 (.86)
Livermild	24 / 557 (4.3)	1.35 (.31)	1.28 (.43)
Diabetesmild	37 / 557 (6.6)	1.34 (.22)	1.31 (.29)
Renal	2 / 557 (0.4)	2.50 (.36)	1.21 (.86)
Diabetessevere	2 / 557 (0.4)	0.55 (.55)	0.58 (.58)
Anytumor	9 / 557 (1.6)	0.73 (.58)	0.75 (.62)
Leukemia	1 / 557 (0.2)	2.48 (.37)	2.00 (.50)
Lymphoma	3 / 557 (0.5)	1.31 (.71)	1.37 (.66)

Table 23. Interactions between each comorbidity and age/race on survival using Cox regression

Interaction of variables-CHF, COPD, LiverMild, DiabetesMild with Age, Race		
Charlson_comorbidity with Univ_P-value<3.0	Multi interaction with Age/Race	HRs (P-value)
CHF	Age,CHF,AGE*CHF	0.99 (.72)
	Black,CHF,Black*CHF	0.38 (.38)
	Age,Black,CHF,Age*Black*CHF	0.99 (.38)
COPD	Age,COPD,Age*COPD	1.02 (.33)
	Black, COPD,Black*COPD	2.39 (.22)
	Age,Black,COPD,Age*Black*COPD	1.01 (.41)
LiverMild	Age,LiverMild,Age*LiverMild	1.01 (.85)
	Black,LiverMild,Black*LiverMild	0.00 (.97)
	Age,Black,LiverMild,Age*Black*LiverMild	0.84 (.97)
DiabetesMild	Age,DiabetesMild,Age* DiabetesMild	1.00 (.82)
	Black,DiabetesMild,Black* DiabetesMild	1.12 (.85)
	Age,Black,DiabetesMild,Age*Black* DiabetesMild	1.00 (.94)

Table 24. Frequency and analysis using accelerated failure-time model for Charlson comorbidity conditions

	Frequency (%)	Univariate_Estimates (P-value)	Multivariate_Estimates (P-value)
MI	6 / 557 (1.1)	-.11 (.77)	-.12(.76)
CHF	13 / 557 (2.3)	-.51 (.09)	-.41(.21)
PVD	2 / 557 (0.4)	16.36(1.0)	16.88(1.0)
CVD	8 / 557 (1.4)	-.25 (.59)	-.38 (.42)
Dementia	1 / 557 (0.2)	15.57(1.0)	16.30(1.0)
COPD	23 / 557 (4.1)	-.21 (.31)	-.21 (.32)
Connectivetissue	4 / 557 (0.7)	-.54 (.34)	-.48 (.40)
Ulcer	4 / 557 (0.7)	-.03 (.95)	.07(.90)
Livermild	24 / 557 (4.3)	-.22 (.35)	-.17 (.48)
Diabetesmild	37 / 557 (6.6)	-.26 (.16)	-.24 (.22)
Renal	2 / 557 (0.4)	-.77 (.33)	-.16 (.85)
Diabetessevere	2 / 557 (0.4)	.48(.55)	.43(.58)
Anytumor	9 / 557 (1.6)	.25(.59)	.22(.63)
Leukemia	1 / 557 (0.2)	-.75 (.35)	-.54 (.51)
Lymphoma	3 / 557 (0.5)	-.19 (.73)	-.23 (.68)

Table 25. Interactions between each comorbidity and age/race on survival using accelerated failure-time model

Interaction of variables-CHF, COPD, LiverMild, DiabetesMild with Age, Race		
Charlson_comorbidity with Univ_P-value<3.0	Multi interaction with Age/Race	Estimates (P-value)
CHF 1.85(.11)	Age,CHF,AGE*CHF	.01(.77)
	Black,CHF,Black*CHF	.74(.40)
	Age,Black,CHF,Age*Black*CHF	.01(.39)
COPD 1.325(.29)	Age,COPD,Age*COPD	-.02 (.34)
	Black, COPD,Black*COPD	-.69 (.21)
	Age,Black,COPD,Age*Black*COPD	-.01 (.41)
LiverMild 1.34(.32)	Age,LiverMild,Age*LiverMild	-.01 (.82)
	Black,LiverMild,Black*LiverMild	15.83(1.0)
	Age,Black,LiverMild,Age*Black*LiverMild	.26(1.0)
DiabetesMild 1.35(.20)	Age,DiabetesMild,Age* DiabetesMild	-.00 (.87)
	Black,DiabetesMild,Black* DiabetesMild	-.08 (.87)
	Age,Black,DiabetesMild,Age*Black* DiabetesMild	-.00 (.95)

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Table 26. Univariate analyses by Cox regression of missing variables (Gths, Income, Catincome, StageIIBMI, CatStageIIBMI, Cat4StageIIBMI, Menopause, Chalson_Index, Hypertension) and corresponding imputed variables (ImpGths, ImpIncome, ImpCatIncome, ImpStageIIBMI, ImpCatStageIIBMI, ImpCat4StageIIBMI, ImpMeno, impCharlson_index, impHypertension) for survival

	Observed value						**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
Variable	**Value**	**N**	**Med**	**Mean (SE)**	**HR (P-value)**		**Value**	**N**	**Med**	**Mean (SE)**	**HR (P-value)**	**Value**	**N**	**Med**	**Mean (SE)**	**HR (P-value)**
Gths	0	238	33.0	41.9 (2.32)	.74 (.02)		0	486	38.0	46.3 (1.76)	.90 (.53)	0	486	38.0	46.3 (1.76)	2.74 (<.00)
	1	248	45.0	46.6 (2.08)	***Long-rank test,*** P=.02		1	71	45.0	45.1 (3.185)	***Long-rank test,*** P=.53	1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*185*					*Missing*	*0*				*Missing*	*71*			
	Total	*671*					*Total*	*557*				*Total*	*671*			
Income	Dollars	360	43.0	47.0 (2.025)	1.00 (.57)		0	360	43.0	47.0 (2.025)	1.08 (.51)	0	360	43.0	47.0 (2.025)	2.92 (<.00)
							1	197	36.0	44.2 (2.52)	***Long-rank test,*** P=.50	1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*311*					*Missing*	*0*				*Missing*	*197*			
	Total	*671*					*Total*	*557*				*Total*	*671*			
CatIncome	1	67	34.0	48.8 (5.56)	1.00	***Long-rank test,*** P=.89	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	133	45.0	45.8 (2.77)	.92 (.69)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	160	40.0	43.8 (2.375)	.98 (.92)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	311					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 26 (Continued)																
	Observed value						**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
	Total	671					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
StageIIBMI	Kg/m^2	443	38.0	44.3 (1.78)	1.01 (.52)		0	443	38.0	44.3 (1.78)	.67 (.01) ***Long-rank test,*** P=.01	0	443	38.0	44.3 (1.78)	2.585 (<.00) ***Long-rank test,*** P=<.00
							1	114	58.0	53.7 (3.47)		1	114	18.0	22.3 (1.63)	
	Missing	*228*					*Missing*	*0*				*Missing*	*114*			
	Total	*671*					*Total*	*557*				*Total*	*671*			
CatStageIIBMI	0	31	58.0	42.3 (4.84)	1.00	***Long-rank test,*** P=.08	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	118	32.0	37.6 (2.64)	1.73 (.06)		N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	
	2	294	40.0	45.6 (2.25)	1.36 (.27)		N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	
	Missing	*228*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cat4StageIIBMI	0	31	58.0	42.3 (4.84)	1.00	***Long-rank test,*** P=.13	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	118	32.0	37.6 (2.64)	1.73 (.06)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	150	41.0	47.2 (3.16)	1.27 (.41)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	144	39.0	39.1 (2.185)	1.45 (.20)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*228*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Menopause	0	101	58.0	53.2 (3.63)	1.35 (.06) ***Long-rank test,*** P=.0555		0	498	43.0	47.2 (1.73)	1.285 (.18) ***Long-rank test,*** P=.17	0	498	43.0	47.2 (1.73)	2.845 (<.00) ***Long-rank test,*** P=<.00
	1	397	39.0	43.0 (1.63)			1	59	29.0	40.3 (4.56)		1	114	18.0	22.3 (1.63)	
	Missing	*173*					*Missing*	*0*				*Missing*	*59*			
	Total	*671*					*Total*	*557*				*Total*	*671*			

Table 26 (Continued)																
	Observed value						**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
CharIson_Index	1-31 Scores	551	40.0	46.4 (1.63)	1.08 (.06)		N/A	N/A	N/A	N/A	N/A	0	551	40.0	46.4 (1.63)	2.77 (<.00)
												1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*120*					N/A	N/A	N/A	N/A	N/A	*Missing*	*6*			
	Total	*671*					N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
Hypertension	0	301	45.0	50.4 (2.16)	1.59 (.00)		0	529	39.0	45.7 (1.67)	.49 (.02)	0	529	39.0	45.7 (1.67)	2.68 (<.00)
	1	228	31.0	35.0 (1.77)	***Long-rank test,*** P=.00		1	28	64.0	56.4 (4.27)	***Long-rank test,*** P=.02	1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*142*					*Missing*	*0*				*Missing*	*28*			
	Total	*671*					*Total*	*557*				*Total*	*671*			
ImpGths	0	270	36.0	42.7 (2.14)	.78 (.03)		N/A	N/A	N/A	N/A	N/A	0	557	40.0	46.5 (1.625)	2.79 (<.00)
	1	287	45.0	46.4 (1.92)	***Long-rank test,*** P=.03		N/A	N/A	N/A	N/A	N/A	1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*114*					N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*					N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpIncome	Dollars	557	40.0	46.5 (1.625)	1.00 (.79)		N/A	N/A	N/A	N/A	N/A	0	557	40.0	46.5 (1.625)	2.79 (<.00)
												1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*114*					N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*					N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpCatIncome	1	71	34.0	48.2 (5.44)	1.00	***Long-rank test,*** P=.96	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	156	45.0	44.6 (2.60)	.945 (.78)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	330	39.0	45.3 (1.88)	.96 (.83)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 26 (Continued)																	
	Observed value						**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
	Missing	114					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	671					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ImpStageIIBMI	Kg/m^2	557	40.0	46.5 (1.625)	1.01 (.51)		N/A	N/A	N/A	N/A	N/A	0	557	40.0	46.5 (1.625)	2.79 (<.00)
												1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*114*					N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*					N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpCatStageIIBMI	0	31	58.0	42.3 (4.84)	1.00	***Long-rank test,*** P=.03	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	118	32.0	37.6 (2.64)	1.70 (.07)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	408	45.0	48.4 (1.95)	1.22 (.48)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*114*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ImpCat4StageIIBMI	0	31	58.0	42.3 (4.84)	1.00	***Long-rank test,*** P=.01	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	118	32.0	37.6 (2.64)	1.71 (.07)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	257	46.0	51.0 (2.46)	1.1 (.74)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	151	39.0	38.8 (2.16)	1.46 (.20)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*114*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*					N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ImpMeno	0	142	47.0	49.5 (3.14)	1.17 (.26) ***Long-rank test,*** P=.25		N/A	N/A	N/A	N/A	N/A	0	557	40.0	46.5 (1.625)	2.79 (<.00)
	1	415	39.0	43.0 (1.58)			N/A	N/A	N/A	N/A	N/A	1	114	18.0	22.3 (1.63)	***Long-rank test,*** P=<.00
	Missing	*114*					N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*					N/A	N/A	N/A	N/A	N/A	*Total*	*671*			

Table 26 (Continued)															
	Observed value					**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
ImpHypertension	0	320	47.0	51.2 (2.08)	1.62 (<.00) ***Long-rank test,*** P=<.00	N/A	N/A	N/A	N/A	N/A	0	557	40.0	46.5 (1.625)	2.79 (<.00) ***Long-rank test,*** P=<.00
	1	237	31.0	35.4 (1.76)		N/A	N/A	N/A	N/A	N/A	1	114	18.0	22.3 (1.63)	
	Missing	*114*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Missing*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*total*	*671*			
ImpCharlson_Index	1-31 Scores	557	40.0	46.5 (1.625)	1.085 (.06)	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	0	557	40.0	46.5 (1.625)	2.79 (<.00) ***Long-rank test,*** P=<.00
											1	114	18.0	22.3 (1.63)	
	Missing	*114*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Missing*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*total*	*671*			

Table 27. Univariate Analyses by Cox regression with complete variables (Age, Black, ER, HER2, Metsite)

		Observed value				Observed Value Among SystemicMissing				Observed Value Among Non-SystemicMissing			
Variable	**Value**	**N**	**Median**	**Mean (SE)**	**HR (P-value)**	**N**	**Median**	**Mean (SE)**	**HR (P-value)**	**N**	**Median**	**Mean (SE)**	**HR (P-value)**
Age	Year	671	33.0	41.6 (1.39)	1.01 (.03)	114	18.0	22.3 (1.63)	1.01 (.30)	557	40.0	46.5 (1.625)	1.01 (.00)
	Total	*671*				*114*				*557*			
Black	0	627	33.0	42.1 (1.43)	1.46 (.07) ***Long-rank test,*** P=.07	106	18.0	22.5 (1.61)	1.25 (.55) ***Long-rank test,*** P=.55	521	41.0	47.0 (1.66)	1.46 (.14) ***Long-rank test,*** P=.14
	1	44	22.0	35.3 (5.39)		8	10.5	18.7 (8.64)		36	36.0	29.4 (3.18)	
	Total	*671*				*114*				*557*			
Metsite	1-7	664	33.0	41.9 (1.40)	1.345 (<.00)	107	18.0	22.1 (1.60)	1.225 (.07)	557	40.0	46.5 (1.625)	1.37 (<.00)
	Missing	*7*				*7*				*0*			
	Total	*671*				*114*				*557*			
ER	1	470	40.0	45.4 (1.64)	1.685 (<.00) ***Long-rank test,*** P=<.00	*N/A*	*N/A*	*N/A*	*N/A*	408	45.0	49.0 (1.85)	1.54 (.00) ***Long-rank test,*** P=.00
	2	196	22.0	32.1 (2.17)		*N/A*	*N/A*	*N/A*	*N/A*	149	26.0	37.6 (2.78)	
	Missing	*5*				*N/A*	*N/A*	*N/A*	*N/A*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*557*			
HER2	1	229	39.0	43.1 (2.02)	1.21 (.08) ***Long-rank test,*** P=.08	*N/A*	*N/A*	*N/A*	*N/A*	192	45.0	47.4 (2.29)	1.28 (.05) ***Long-rank test,*** P=.05
	2	422	33.0	40.5 (1.74)		*N/A*	*N/A*	*N/A*	*N/A*	365	38.0	43.9 (1.975)	
	Missing	*20*				*N/A*	*N/A*	*N/A*	*N/A*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*557*			

Table 28. Univariate analyses by accelerated failure-time model of missing variables (Gths, Income, Catincome, StageIIBMI, CatStageIIBMI, Cat4StageIIBMI, Menopause, Chalson_Index, Hypertension) and corresponding imputed variables (ImpGths, ImpIncome, ImpCatIncome, ImpStageIIBMI, ImpCatStageIIBMI, ImpCat4StageIIBMI, ImpMeno, impCharlson_index, impHypertension) for survival

	Observed value					Missing(1) vs. NonMissing(0) among Non-systemic Missing					Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)				
Variable	**Value**	**N**	**Estimate***	**Exponential estimate****	**P-value**	**Value**	**N**	**Estimate***	**Exponential estimate****	**P-value**	**Value**	**N**	**Estimate***	**Exponential estimate****	**P-value**
Gths	0	238	ref	1.00	.02	0	486	ref	1.00	.58	0	486	ref	1.00	<.00
	1	248	.24	1.27		1	71	.08	1.08		1	114	-.81	.44	
	Missing	*185*				*Missing*	*0*				*Missing*	*71*			
	Total	*671*				*Total*	*557*				*Total*	*671*			
Income	Dollars	360	-.00	1.00	.53	0	360	ref	1.00	.58	0	360	ref	1.00	<.00
						1	197	-.05	.95		1	114	-.82	.44	
	Missing	*311*				*Missing*	*0*				*Missing*	*197*			
	Total	*671*				*Total*	*557*				*Total*	*671*			
CatIncome	1	67	ref	1.00		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	133	.06	1.06	.70	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	160	.01	1.01	.95	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*311*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
StageIIBMI	Kg/m^2	443	-.01	.99	.45	0	443	ref	1.00	.01	0	443	ref	1.00	<.00
						1	114	.33	1.39		1	114	-.75	.47	
	Missing	*228*				*Missing*	*0*				*Missing*	*114*			
	Total	*671*				*Total*	*557*				*Total*	*671*			
Cat4StageIIBMI	0	31	ref	1.00		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	118	-.45	.64	.04	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	150	-.21	.81	.35	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	144	-.32	.73	.15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*228*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Menopause	0	101	ref	1.00	.04	0	498	ref	1.00	.16	0	498	ref	1.00	<.00
	1	397	-.25	.78		1	59	-.20	.82		1	114	-.84	.43	
	Missing	*173*				*Missing*	*0*				*Missing*	*59*			

Table 28. (Continued)

	Observed value					**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
	Total	*671*				*Total*	*557*				*Total*	*671*			
CharIson_Index	1-31 Scores	551	-.07	.93	.04	N/A	N/A	N/A	N/A	N/A	0	551	ref	1.00	<.00
						N/A	N/A	N/A	N/A	N/A	*1*	114	-.82	.44	
	Missing	*120*				N/A	N/A	N/A	N/A	N/A	*Missing*	*6*			
	Total	*671*				N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
Hypertension	0	301	ref	1.00	<.00	0	529	ref	1.00	.03	0	529	ref	1.00	<.00
	1	228	-.38	.68		1	28	.55	1.73		1	114	-.80	.45	
	Missing	*142*				*Missing*	*0*				*Missing*	*28*			
	Total	*671*				*Total*	*557*				*Total*	*671*			
ImpGths	0	270	ref	1.00	.03	N/A	N/A	N/A	N/A	N/A	0	557	ref	1.00	<.00
	1	287	.21	1.23		N/A	N/A	N/A	N/A	N/A	1	114	-.82	.44	
	Missing	*114*				N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*				N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpIncome	Dollars	557	-.00	1.00	.72	N/A	N/A	N/A	N/A	N/A	0	557	ref	1.00	<.00
						N/A	N/A	N/A	N/A	N/A	1	114	-.82	.44	
	Missing	*114*				N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*				N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpCatincome	1	71	ref	1.00		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	156	.04	1.04	.79	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	330	.03	1.03	.82	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*114*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ImpStageIIBMI	Kg/m^2	557	-.01	.99	.44	N/A	N/A	N/A	N/A	N/A	0	557	ref	1.00	<.00
						N/A	N/A	N/A	N/A	N/A	1	114	-.82	.44	
	Missing	*114*				N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*				N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpCat4StageIIBMI	0	31	ref	1.00		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	118	-.46	.63	.04	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	257	-.10	.90	.66	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3	151	-.34	.71	.14	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Missing	*114*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	*671*				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 28 (Continued)															
	Observed value					**Missing(1) vs. NonMissing(0) among Non-systemic Missing**					**Systemic Missing (1) vs. Complete Variables among Non-SystemicMissing(0)**				
ImpMeno	0	142	ref	1.00	.22	N/A	N/A	N/A	N/A	N/A	0	557	ref	1.00	<.00
	1	415	-.13	.88		N/A	N/A	N/A	N/A	N/A	1	114	-.82	.44	
	Missing	*114*				N/A	N/A	N/A	N/A	N/A	*Missing*	*0*			
	Total	*671*				N/A	N/A	N/A	N/A	N/A	*Total*	*671*			
ImpHypertension	0	320	ref	1.00	<.00	N/A	N/A	N/A	N/A	N/A	0	557	ref	1.00	<.00
	1	237	-.39	.68		N/A	N/A	N/A	N/A	N/A	1	114	-.82	.44	
	Missing	*114*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Missing*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*total*	*671*			
ImpCharlson_Index	1-31 Scores	557	-.07	0.93	.04	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	0	557	ref	1.00	<.00
											1	114	-.82	.44	
	Missing	*114*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*Missing*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*total*	*671*			

Table 29. Univariate Analyses by accelerated failure-time model with complete variables (Age, Black, ER, HER2, Metsite)

		Observed value				Observed Value Among SystemicMissing				Observed Value Among Non-SystemicMissing			
Variable	**Value**	**N**	**Estimate***	**Exponential Estimate****	**P-value**	**N**	**Estimate***	**Exponential Estimate****	**P-value**	**N**	**Estimate***	**Exponential Estimate****	**P-value**
Age	Year	671	-.01	.99	.02	114	-.01	.99	.30	557	-.01	.99	.00
	Total	*671*				*114*				*557*			
Black	0	627	ref	1.00	.05	106	ref	1.00	.84	521	ref	1.00	.11
	1	44	-.33	.72		8	-.05	.95		36	-.32	.73	
	Total	*671*				*114*				*557*			
Metsite	1-7	664	-.24	.79	<.00	107	-.15	.86	.04	557	-.25	.78	<.00
	Missing	*7*				*7*				*0*			
	Total	*671*				*114*				*557*			
ER	1	470	ref	1.00	<.00	*N/A*	*N/A*	*N/A*	*N/A*	408	ref	1.00	.00
	2	196	-.40	.67		*N/A*	*N/A*	*N/A*	*N/A*	149	-.32	.73	
	Missing	*5*				*N/A*	*N/A*	*N/A*	*N/A*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*557*			
HER2	1	229	ref	1.00	<.0555	*N/A*	*N/A*	*N/A*	*N/A*	192	ref	1.00	.04
	2	422	-.16	.85		*N/A*	*N/A*	*N/A*	*N/A*	365	-.20	.82	
	Missing	*20*				*N/A*	*N/A*	*N/A*	*N/A*	*0*			
	Total	*671*				*N/A*	*N/A*	*N/A*	*N/A*	*557*			

APPENDIX B

SUPPLEMENTAL TABLES AND FIGURES FOR SPECIFIC AIM 2

B.1 FREQUENCY DISTRIBUTIONS OF PREDICTOR VARIABLES BETWEEN PATIENTS WITH MISSING INFORMATION AND PATIENTS WITHOUT MISSING INFORMATION FOR TREATMENT

Table 30. Frequency distributions of predictor variables between patients (n=4) with missing information and patient (n=553) with non-missing information for treatment

Variable	553 patients	4 patients
Age (Mean age in years)	56	47
Race		
Non-Black	517	4
Black	36	0
Education		
<=High School	270	0
> High School	283	4
Median Household Income (Mean of Median Household Income)	$ 40906.1	$ 42299.9
BMI		
Mean of BMI	28.03	27.86
≤20 kg/m^2	31	0
20-24.9 kg/m^2	118	0
25-29.9 kg/m^2	253	4
≥30 kg/m^2	151	0
Menopausal status (P=0.053)		
Pre menopause	139	3
Post menopause	414	1
History of hypertension		
No	316	4
Yes	237	0

Table 30 (Continued)

Variable	553 patients	4 patients
Charlson comorbidity score		
0	439	4
1	15	0
2	32	0
3+	67	0
Charlson Comorbidity Condition		
Myocardial infarct	6	0
Congestive heart failure	13	0
Peripheral vascular disease	2	0
Cerebrovascular disease	8	0
Dementia	1	0
Chronic pulmonary disease	23	0
Connective Tissue disease	4	0
Ulcer disease	4	0
Mild liver disease	24	0
Diabetes	37	0
Moderate or severe renal disease	2	0
Diabetes with end organ damage	2	0
Any Tumor	9	0
Leukemia	1	0
Lymphoma	3	0
ER/PR status		
ER/PR positive	404	4
ER/PR negative	149	0
HER2 status		
HER2 positive	191	1
HER2 negative	362	3
Number of metastatic sites		
1	340	4
2	137	0
3+	76	0
Metastatic location		
Brain	34	0
Bone	298	3
Liver	116	0
Other	308	1

B.2 PATIENTS WITH MISSING INFORMATION FOR TREATMENT

Table 31. Patients with missing information for treatment

Treatment	Treatment delay	ID	Data analysis
Any treatment	missing → 1st treatment	407,451,666	Excluded
	missing → obs. → 1st treatment	502	Delayed treatment (at least)
	obs. → missing → 1st treatment	550	Delayed treatment (at least)
	obs. → missing → obs → 1st treatment	223,372	Delayed treatment (at least)
No any treatment	obs. till study ending or death	115,221,356,517,603	Delayed treatement
	obs. → missing till study ending or death	76,198, 214, 310,366,400	Delayed treatment (at least)
	obs. → missing → obs →missing till study ending or death	226	Delayed treatment (at least)
	missing till study ending or death	667	Excluded

B.3 LML FUNCTION AT MEAN OF TREATMENT DELAY

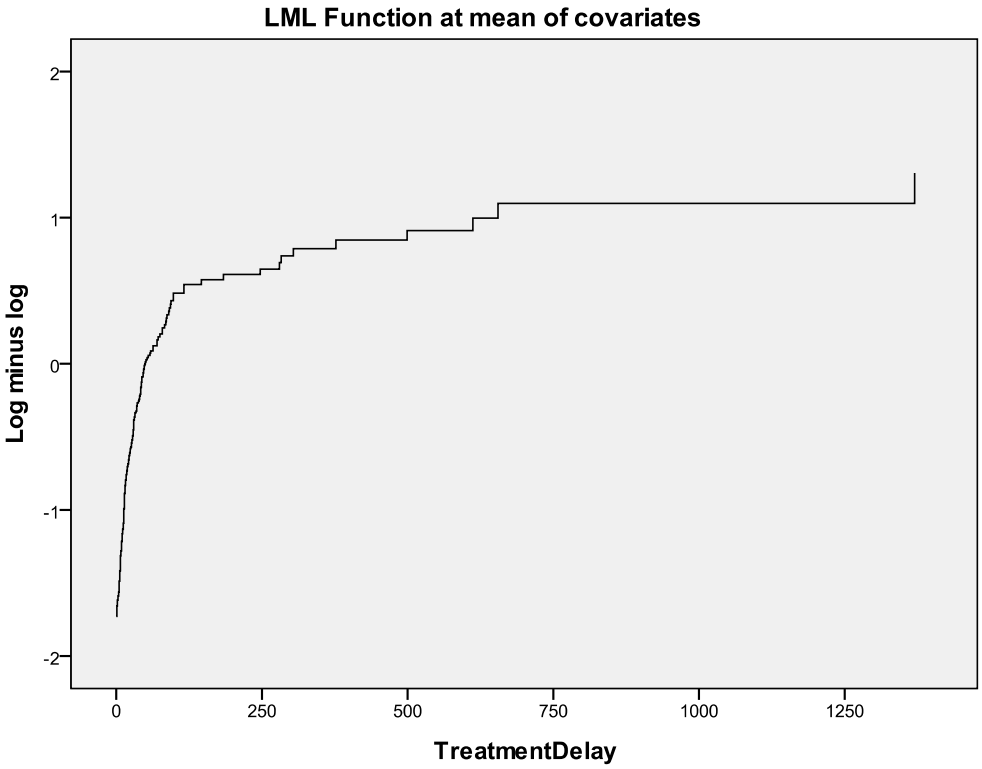


Figure 16. Log minus log function at mean of treatment delay as a continuous variable

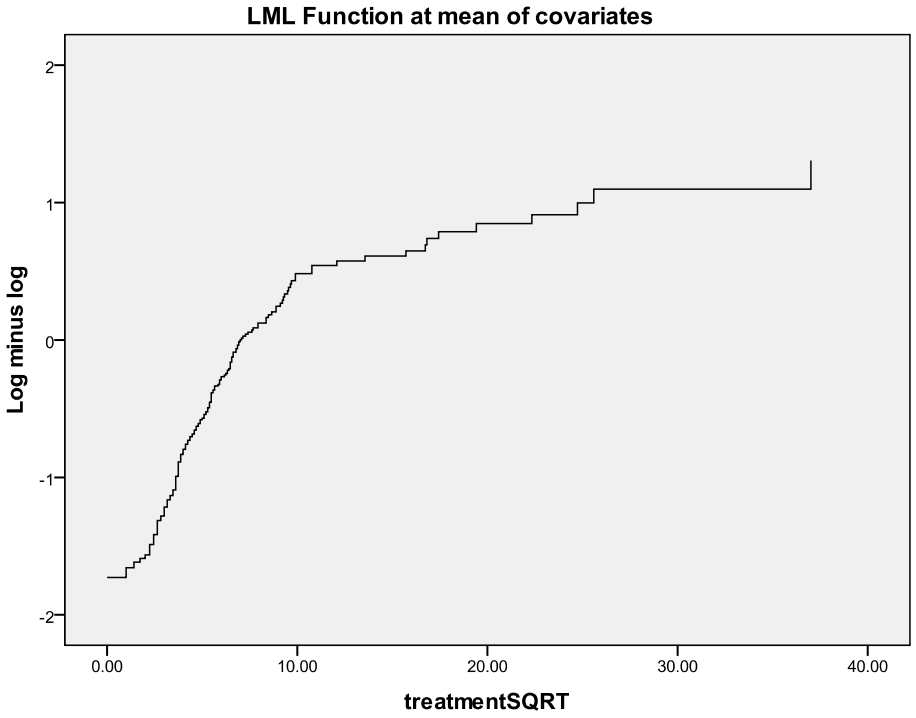


Figure 17. Log minus log function at mean of square root of treatment delay

B.4 COX REGRESSION ANALYSIS OF TREATMENT DELAY PERCENTILE FOR SURVIVAL MEASURED FROM METASTASIS AND FROM FIRST TREATMENT

Table 32. Cox regression analysis of treatment delay percentile for survival from metastatic breast cancer diagnosis

Survival measured from metastatic breast cancer diagnosis							
		Univariate analysis			Multivariate analysis*		
Variable	Patients No. (%)	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Treatment delay Percentile	553 (100.0)						
70 percentile	390 (70.5)	1.07	0.78-1.45	0.680	1.05	0.77-1.44	0.758
70-90 percentile	107 (19.4)	1.00	referent		1.00	referent	
90-100 percentile	56 (10.1)	1.20	0.76-1.87	0.435	1.02	0.62-1.66	0.945

Table 33. Cox regression analysis of treatment delay percentile for survival from first treatment

Survival measured from first treatment							
		Univariate analysis			Multivariate analysis**		
Variable	Patients No. (%)	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Treatment delay	539 (100.0)						
70 percentile	379 (70.3)	1.15	0.84-1.57	0.378	1.11	0.80-1.52	0.537
70-90 percentile	105 (19.5)	1.00	referent		1.00	referent	
90-100 percentile	55 (10.2)	1.44	0.90-2.31	0.130	1.36	0.81-2.27	0.241

B.5 COX REGRESSION ANALYSIS OF TREATMENT DELAY (≤4 WEEK, 4–12 WEEK, 12–24 WEEK, >24 WEEK) FOR SURVIVAL MEASURED FROM METASTASIS AND FROM FIRST TREATMENT

Table 34. Cox regression analysis between treatment delay (≤4 week, 4–12 week, 12–24 week, >24 week) and survival from metastatic breast cancer in patients (n = 553) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Survival measured from metastatic breast cancer diagnosis							
		Univariate analysis			Multivariate analysis*		
Variable	Patients No. (%)	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Treatment delay	553 (100.0)			0.031†			0.065†
≤4 week	390 (70.5)	1.11	0.83-1.48	0.483	1.12	0.83-1.52	0.450
4–12 week	129 (23.3)	1.00	referent		1.00	referent	
12-24 week	18 (3.3)	2.49	1.33-4.65	0.004	2.13	1.12-4.06	0.021
>24 week	16 (2.9)	1.08	0.55-2.12	0.813	0.71	0.35-1.44	0.342

Abbreviation: 95% CI, 95% Confidence Interval.
* Cox regression was performed for examining the effect of treatment delay on survival, adjusted by covariates (BMI, history of hypertension, ER/PR status, HER2 status, number of metastatic sites, brain, bone and liver metastasis), selected to be significant with P-value <0.05 by backward stepwise selection.
† P-value for omnibus test.

Table 35. Cox regression analysis between treatment delay (≤4 week, 4–12 week, 12–24 week, >24 week) and survival from first treatment in patients* (n = 539) with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

Survival measured from first treatment							
		Univariate analysis			Multivariate analysis**		
Variable	Patients No. (%)	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Treatment delay	539 (100.0)			0.021†			0.098†
≤4 week	388 (71.9)	1.10	0.82-1.47	0.537	1.06	0.78-1.43	0.727
4–12 week	125 (23.2)	1.00	referent		1.00	referent	
12-24 week	16 (3.0)	2.74	1.39-5.39	0.004	2.39	1.19-4.77	0.014
>24 week	10 (1.9)	1.41	0.61-3.28	0.423	1.21	0.51-2.87	0.669

Abbreviation: 95% CI, 95% Confidence Interval.
* Patients (n=14 among 553) censored their treatment interval until death or end of study were excluded from analysis.
** Cox regression was performed for examining the effect of treatment delay on survival, adjusted by covariates (BMI, history of hypertension, ER/PR status, HER2 status, number of metastatic sites, and liver metastasis), selected to be significant with P-value <0.05 by backward stepwise selection.
† P-value for omnibus test.

APPENDIX C

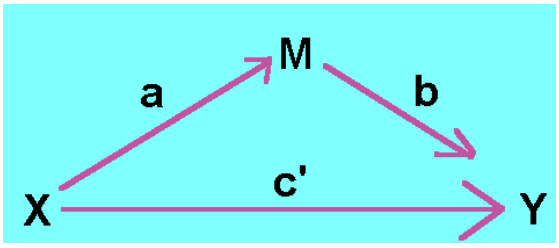
SUPPLEMENTAL TABLES AND FIGURES FOR SPECIFIC AIM 3

C.1 ASSESSMENT OF POTENTIAL MEDIATOR VARIABLE: BARON AND KENNY STEPS

Panel A

C= total effect

Panel B



C'=direct effect, C-C'≈a*b =indirect effect

Baron and Kenny steps

- Step 1: testing c
- Step 2: testing a
- Step 3: testing b

Assessed by equations:

Y = i1 + cX (step 1)

M= i2 + aX (step 2)

Y = i3 + c'X + bM (step 3)

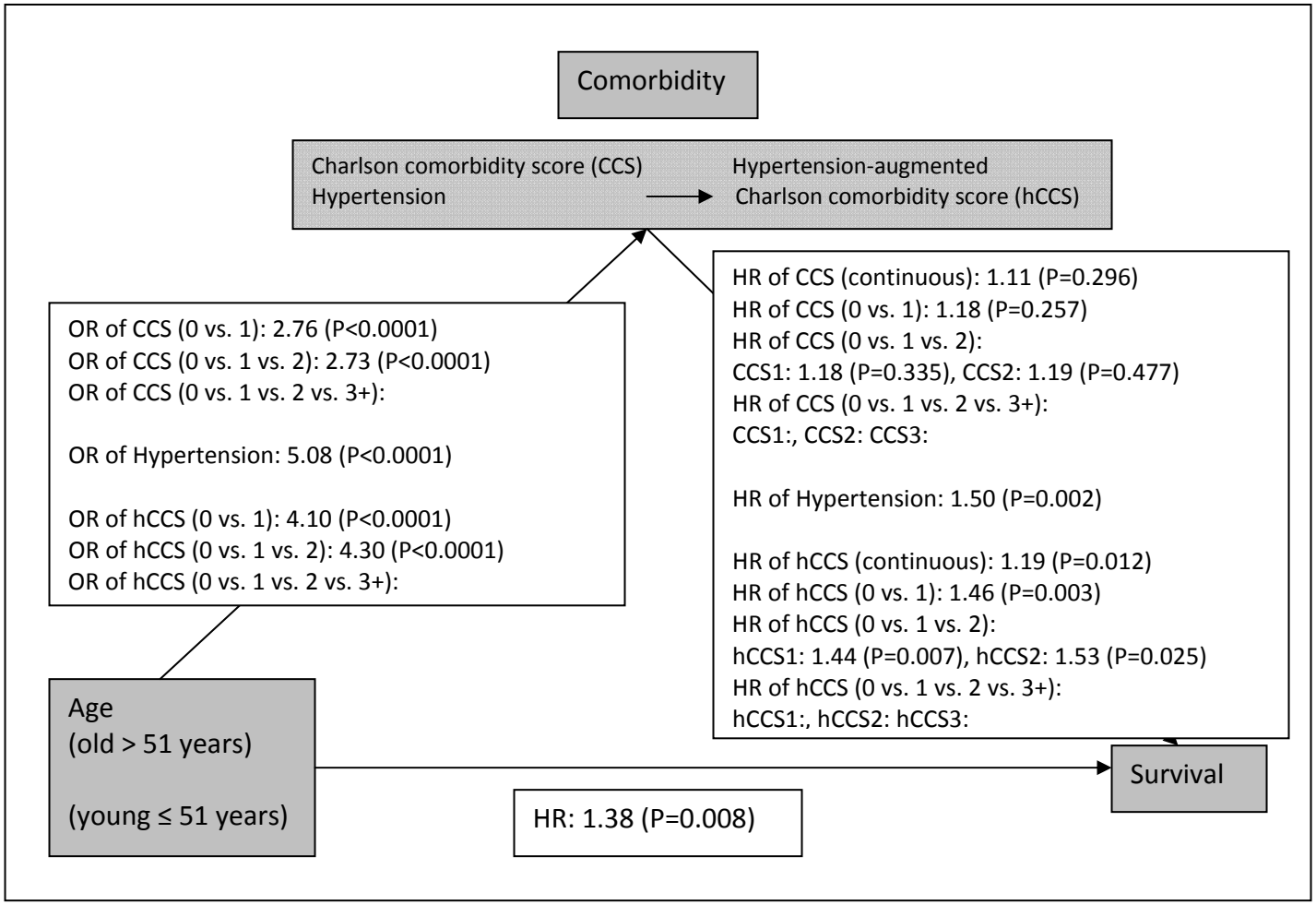


Figure 18. Diagram for the association of comorbidity with age-survival relationship based on univariate analysis using Cox regression and logistic regression model

C.2 COVARIATES TO BE ADJUSTED IN MULTIVARIATE ANALYSIS

Table 36. Covariates to be adjusted in multivariate analysis

	no.	variable	value
Patient ID	1	ID	553 patients
Outcome variable	1	Status	event (0 censored, 1 dead)
	2	Msurv	survival length in month
Independent variable	1	Age	categorical variable (0, =< 51 years; 1, > 51 year)
Mediator variable	1	C2CCS	Charlson Comorbidity Score, categorical variable (0, 0 score; 1, >0 score)
	2	ImpHypertension	Hypertension (0, no of hypertension; 1, yes of hypertension)
	3	C2HCCS	Hypertension augmented Charlson Comorbidity Score, categorical variable (0, 0 score; 1, >0 score)
Covariates	1	Black	race (0, non-black; 1, black)
	2	ImpGths	education (0, =< high school; 1, > high school)
	3	ImpER	ER/PR status (0, positive; 1, negative)
	4	ImpHER2	HER2 status (0, positive; 1, negative)
	5	Metsite	continuous variable (0,1,2, ect.)
	6	Metloc1	Metastatic location (Brain) at the initial metastasis diagnosis-Brain (0, no; 1, yes)
	7	Metloc2	Metastatic location (Bone) at the initial metastasis diagnosis-Bone (0, no; 1, yes)
	8	Metloc4	Metastatic location (Liver) at the initial metastasis diagnosis-Liver (0, no; 1, yes)
	9	Tr	Treatment delay categorized into three groups (0,=<28 days; 1, 28<-84 days; 2, >84 days)

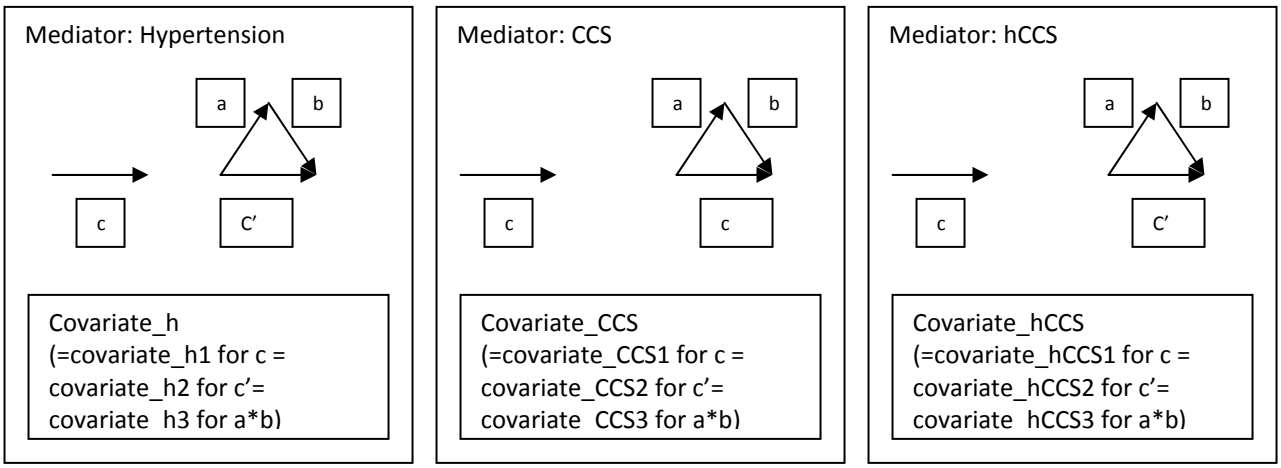


Figure 19. Covariates to be adjusted in multivariate analysis of each step (c, c', and a*b) of Baron Kenny approach for hypertension, CCS, and hCCS related to survival

➔ covariate_h1=covariate_h2=covariate_h3;
covariate_CCS1=covariates_CCS2=covariate_CC3;
covariate_hCCS1=covariate_hCCS2=covariate_hCCS3.

➔ covariates_h=covariate_CCS=covariate_hCCS.

C.3 FREQUENCY DISTRIBUTIONS OF COMORBIDITIES BY AGE

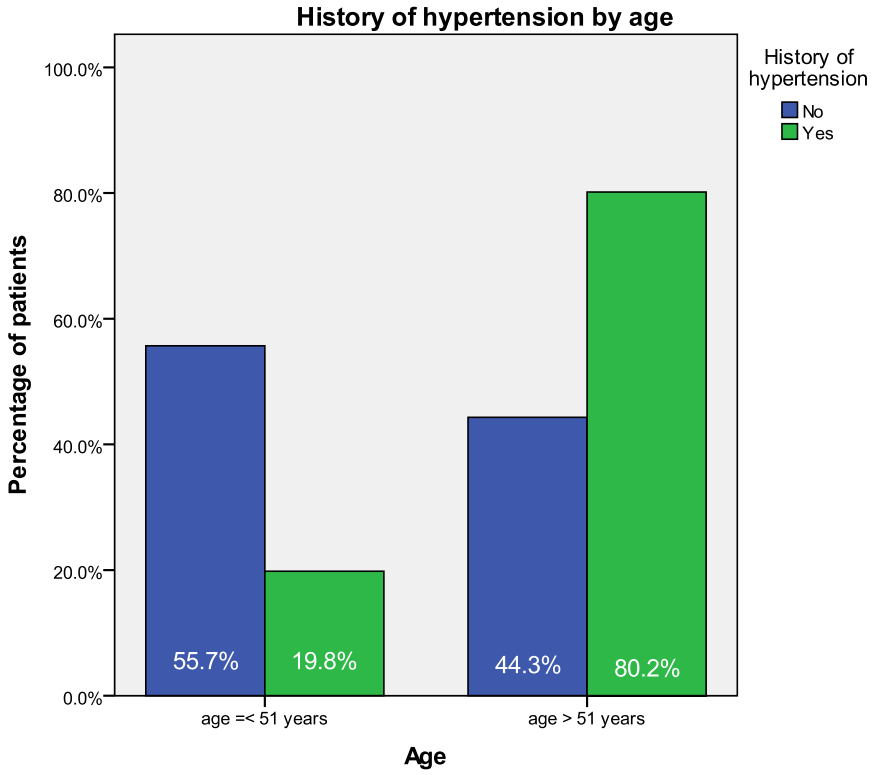


Figure 20. Frequency distribution of hypertension by age in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

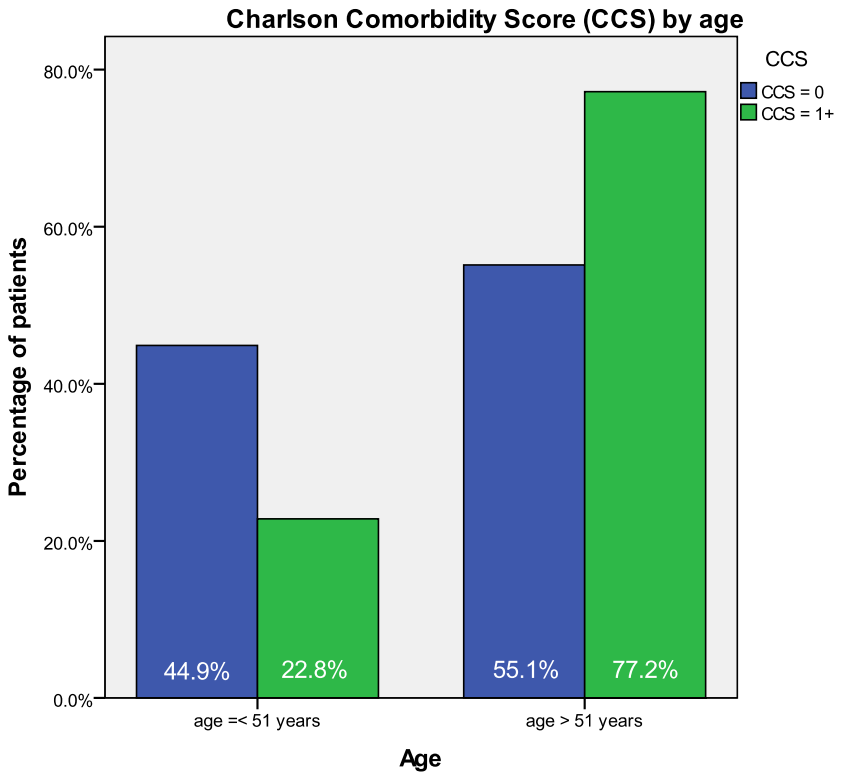


Figure 21. Frequency distribution of CCS by age in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

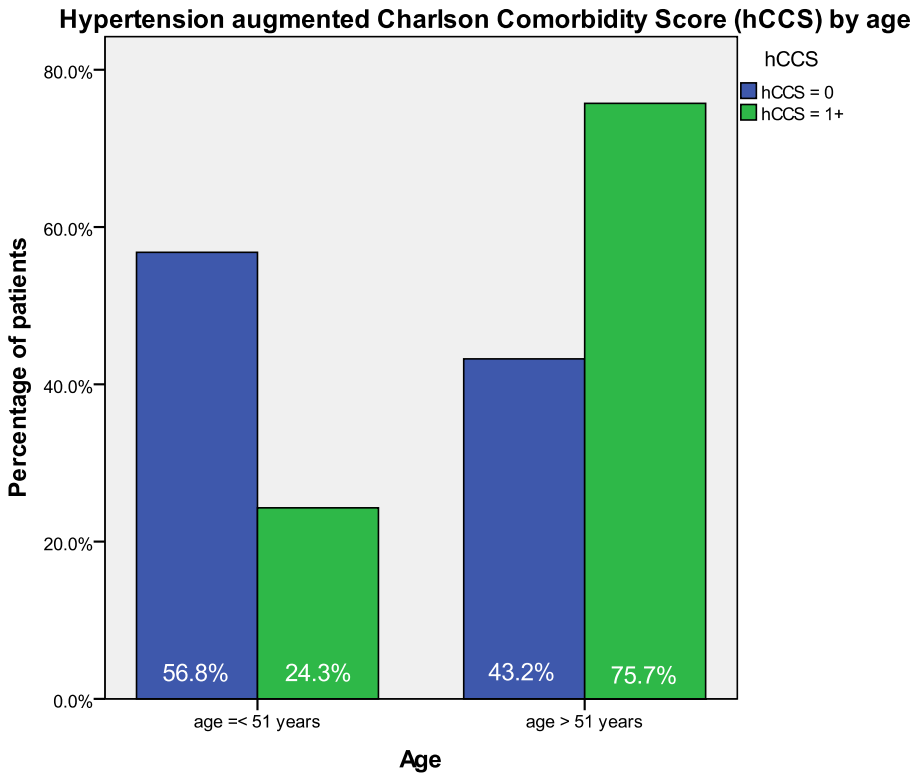


Figure 22. Frequency distribution of hCCS by age in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

C.4 KAPLAN-MEIER'S CURVES OF SURVIVAL BY COMORBIDITIES

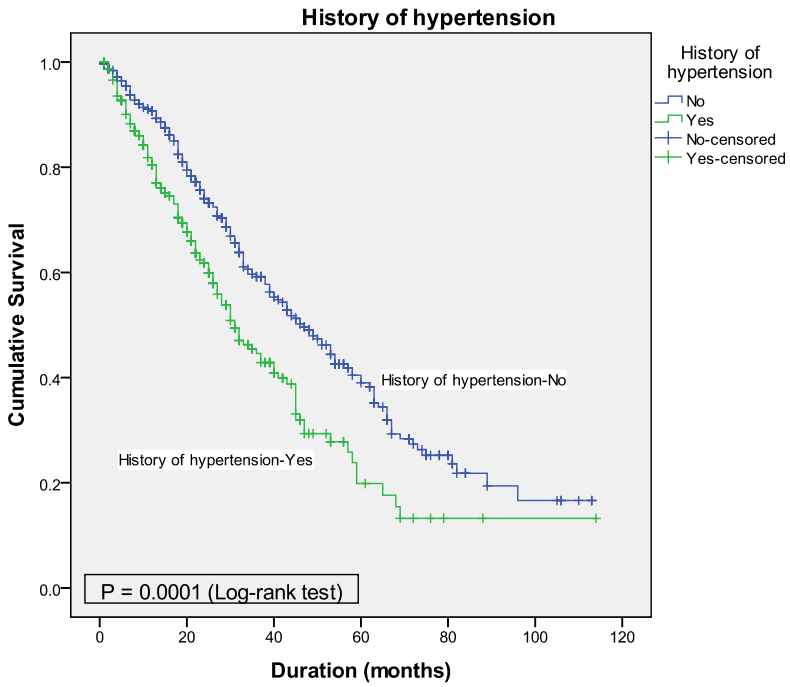


Figure 23. Kaplan-Meier's curve of survival by history of hypertension in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

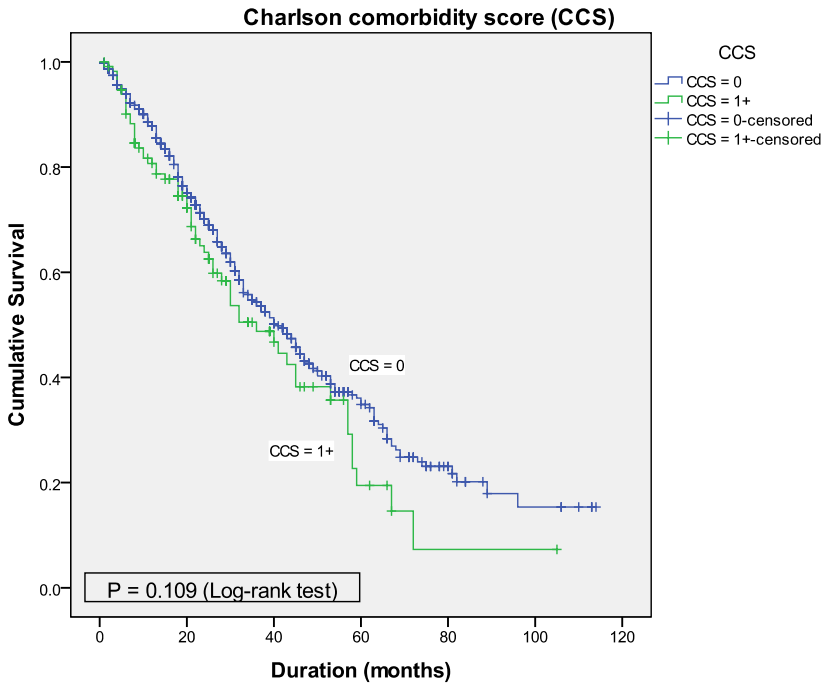


Figure 24. Kaplan-Meier's curve of survival by Charlson Comorbidity Score (CCS) in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

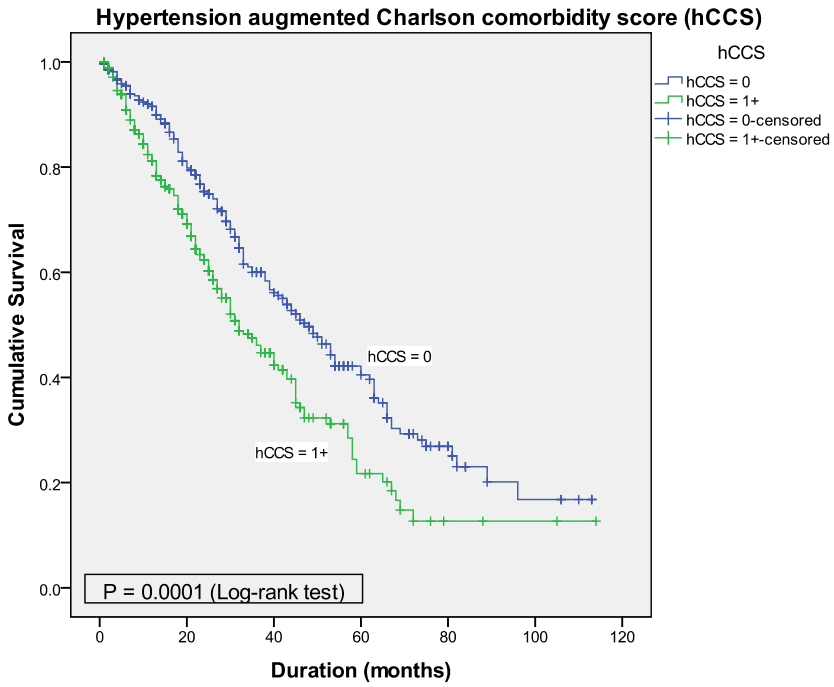


Figure 25. Kaplan-Meier's curve of survival by hypertension augmented Charlson Comorbidity Score (hCCS) in patients with metastatic breast cancer identified at two sites of the UPMC, UPCI Breast Cancer Program

C.5 DIAGRAMS FOR ASSOCIATIONS OF COMORBIDITIES WITH AGE-SURVIVAL RELATIONSHIP

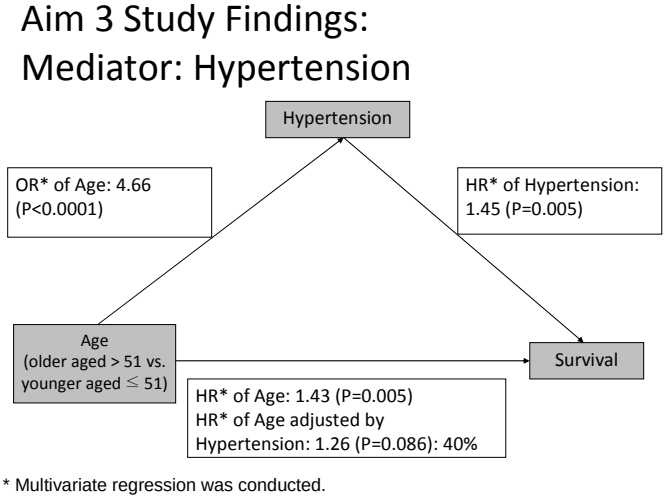


Figure 26. Hypertension as a mediator of age-survival relationship

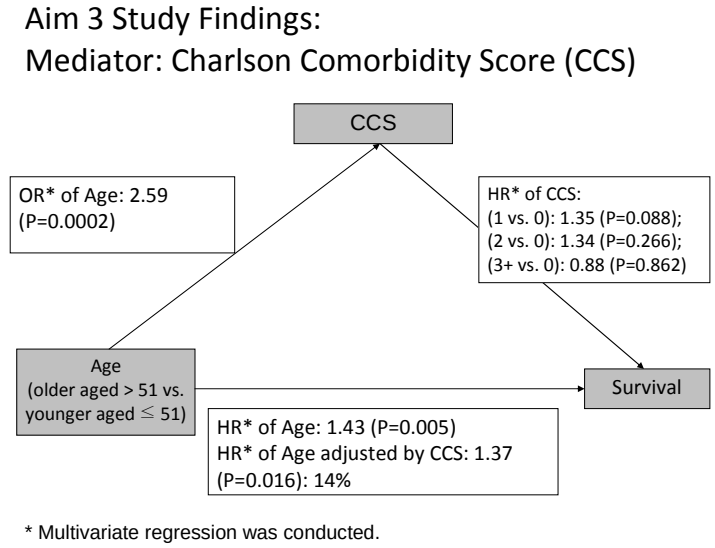


Figure 27. CCS as a mediator of age-survival relationship

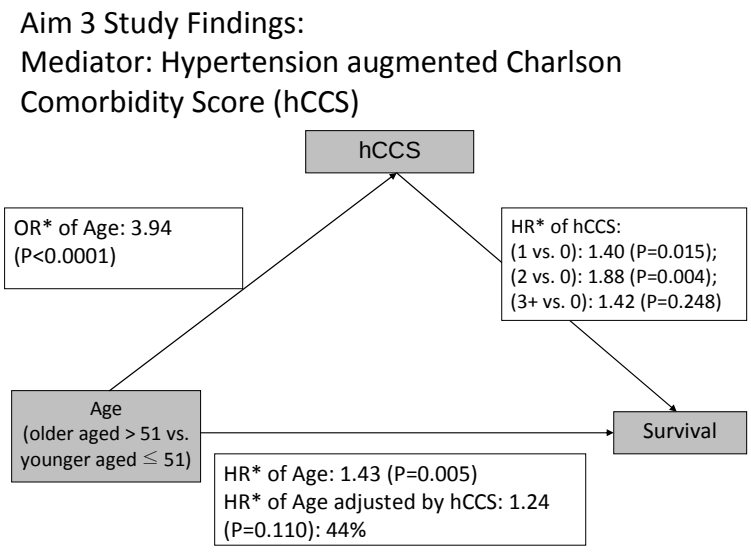


Figure 28. HCCS as a mediator of age-survival relationship

Table 37. Proportion of indirect effect (c-c') of comorbidity among total effect (c) for age-survival relationship (Accelerated failure time model vs. Cox regression model)

(Total effect– Direct effect) /Total effect	Method	Accelerated failure time model	Cox regression model	Cox regression model
	Parameter	(c-c')/c	(HR(c)-HR(c')) /(HR(c)-1)	(c-c')/c
Mediator	Hypertension	33%	40%	34%
Mediator	C4CCS	12%	14%	12%
Mediator	C4HCCS	37%	44%	39%

APPENDIX D

METASTATIC BREAST CANCER (MBC) STUDY DATA COLLECTION AND MEDICAL RECORD ABSTRACTION PROCEDURE AND MISSING DATA

D.1 MBC STUDY CODING SHEET

Table 38. MBC Study coding sheet

CODING SHEET (MBC STUDY)		
Status		Update (OCT/10)
	0	Alive
	1	Deceased
Age		
		Subject's age at MetDX
Race		
	1	Caucasian
	2	African American
	3	Asian- this includes China, Japan, Turkey, Iran, Iraq, etc.
	4	Hispanic
	5	Other (ex., American Indian/Alaska Native)
Sites		
		Number of metastatic sites as of current update date
LocMets		
		Location of Metastatic sites
MoMet		
		Months from diagnosis to metastatic disease
ER		
	1	ER and/or PR positive
	2	Neither ER nor PR positive
	-1	Unknown (both ER and PR unknown)
HER2		
	1	HER2 positive
	2	Her2 negative
	-1	Unknown
Msurv		
		Number of months from MetDX to current update date if alive or CTB date if deceased.
Bcsurv		
		Total months of breast cancer survival. Only used for CTB subjects. Leave blank in alive subjects.
		Bcsurv = MoMet + Msurv.
Tx1wait_Missing		
	1	Patient have missing information for treatment during the time between the date of metastasis and the date of the first treatment of metastasis
	-1	Patient do not have missing information for treatment during the time between the date of metastasis and the date of the first treatment of metastasis
Tx_		**Overall treatment category**
	-1	No information of treatment on medical records
	1	Observation
	2	Chemotherapy Alone
	3	Chemo + Herceptin
	4	Herceptin Alone
	5	Hormonal Therapy Alone
	6	Hormonal Therapy + Chemo
	7	Hormonal Therapy, Chemo + Herceptin
	8	Immunologic Therapy
	9	Hormonal Therapy + Herceptin

Table 38 (Continued)

CODING SHEET (MBC STUDY)

	10	Vaccine + Chemo
	11	Vaccine + Hormonal Therapy
	12	Vaccine Alone
	13	Herceptin + Biologic Chemo (4,8)
	14	Herceptin, Biologic Chemo + Hormonal Therapy
	15	Trial: UPCI-02-106
	16	Trial: AMG-162
	17	Clinical trial w/ Chemo (e.g., chemo vs. placebo)
	18	UPCI 06-042
	19	Biologic Chemo + Hormonal Therapy
Mo		
		monthly based period during the treatment
PS		**ECOG Pain Score:**
	1	If ECOG is 0 or 1
	2	If ECOG is greater than 1
Tx CHANGE		**Was there a Tx Change?**
	1	Yes
	2	No
REASON		**What prompted the Tx change?**
	1	Radiographic Progression
	2	Toxicity
	3	Clinical Progression

TX_Chemo	**Chemotherapy Codes**	**TX_Horm**	**Hormonal Therapy Codes**
1	Adriamycin	1	Tamoxifen
2	Cytoxan	2	Femera
3	5-FU	3	Megace
4	Methotrexate	4	Arimidex
5	Navelbine	5	Lupron
6	Xeloda	6	Aromasin
7	Taxol	7	Zoladex
8	Taxotere	8	Raloxifine
9	Mitoxantrone	9	Faslodex
10	Gemzar	10	Fareston
11	Carboplatinum	11	Fulvestrant
12	Epirubicin	12	Femara/Lupron
13	Doxil	13	Arimidex/Femera
14	Veg F.	14	Arimidex/Lupron
15	Theraptope	15	Aromasin/Faslodex
16	Leukovorin	16	Faslodex/Tamoxifen
17	Epitholone B	17	Arimadex/Faslodex
18	Cisplatin	18	Lupron/Tamoxifen
19	Carbo/Taxol	19	Faslodex/Lupron
20	Taxotere/Xeloda	20	Aromasin/Lupron
21	Carbo/Taxotere	21	Faslodex/Femara
22	Adriamycin/Cytoxan	22	Lupron/Megace/Tamoxifen
23	Gemzar/Taxotere	23	Megace/Tamoxifen
24	Adriamycin/Cytoxan/Taxotere	24	same as 15
25	TPA-Alteplase	25	Arimidex/Aromasin

Table 38 (Continued)

CODING SHEET (MBC STUDY)

26	Cytoxan/Methotrexate/5-FU
27	Cytoxan/Epirubicin/5-FU
28	Epitholone/Xeloda
29	Adriamycin/Taxotere
30	Abraxane
31	Gemzar/Taxol
32	Leukovorin/Mitoxantrone/5-FU
33	Cytoxan/Epirubicin
34	Gemzar/Navalbene
35	Epirubicin/Taxotere
36	Adriamycin/Cisplatin/Cytoxan
37	Carbo/Gemzar/Taxol
38	Temodar
39	Veg F/Xeloda
40	Carbo/Taxol/Taxotere
41	Gemzar/Mitoxantrone
42	Cisplatin/Gemzar
43	Leukovorin/5-FU
44	Gemzar/Xeloda
45	Carbo/Taxotere/Xeloda
46	Navelbine/Taxotere
47	Gemzar/Abraxane
48	Carbo/Gemzar/Taxotere
49	Carbo/Gemzar
50	Adriamycin/Cytoxan/5-FU
51	Camptosar
52	Carbo/Gemzar/Navelbine/Taxotere
53	SB-715992
54	Temodar
55	Chemo vs. Placebo
56	Lapatinib vs. Placebo
57	Taxol & Xeloda
58	Carbo & Abraxane
59	Abraxane & Mitox
60	Xeloda & Bevacizumab vs. placebo
61	Lapatinib vs. Placebo and Xeloda
62	Lapatinib (Tykerb)
63	Lapatinib/Abraxane
64	Triapine
65	CPT-11
66	Sutent (Sunitnib)
67	Lxabepilone (Ixempra)
68	Navelbine + Xeloda
69	Navelbine + Gemzar + Taxol
70	Xeloda + Carbo + Abraxane + Lapatinib
71	Navelbine + Lapatinib
72	Xeloda + Mitoxantrone
73	Xeloda+ Abraxane

26	Arimidex/Megace
27	Aromasin/Megace
28	Lupron/Megace/Tamoxifen
29	Faslodex/Lupron/Megace
30	Fareston/Zoladex
31	Femara/Zoladex
32	Arimadex/Zoladex
33	Megace/Zoladex
34	Tamoxifen/Aromasin
35	Faslodex/Megace
36	Faslodex/Femara/Megace
37	Tamoxifen/Zoladex
38	Arimidex/Tamoxifen
39	Femara/Lupron/Megace
40	Femara/Megace
41	Aromasin/Zoladex
42	Faslodex/Femara/Lupron
43	Aromasin/Faslodex/Lupron
44	Faslodex/Megace/Tamoxifen
45	Tamoxifen + Aromasin + Faslodex
46	Tamoxifen + Arimadex + Lupron
47	Aromasin + Zoladex + Faslodex
48	Zoladex + Faslodex
49	Tamoxifen + Femera
50	Megace + Lupron
51	Megace + Aromasin + Faslodex
52	Femera + Aromasin
53	Tamoxifen + Lupron + Faslodex
54	Tamoxifen + Femera + Faslodex
55	Femera + Arimadex + Lupron
56	Aromasin + Fareston
57	Arimadex + Lupron + Faslodex
58	Faslodex + Fareston
59	Arimadex + Aromasin + Faslodex
60	Tamoxifen + Zoladex + Faslodex
61	TAS-108
62	Arimidex + Zoladex + Faslodex

Support	**Supportive Care Codes (in abstracts)**
1	Pamidronate (Aredia)
2	Local Radiation
3	Gamma Knife
4	Strontium
5	Sumarium
6	Zometa (zoledronate)
7	RBC
8	Whole Brain XRT
9	Cyberknife

Table 38 (Continued)

CODING SHEET (MBC STUDY)

74	Navelbine + Gemzar
75	Xeloda + Carboplatinum
76	Xeloda + Temodar + Lapatinib
77	5-FU + Taxotere
78	Navelbine + Abraxane
79	Adriamycine + Xeloda + Taxotere
80	Navelbine + Doxil
81	Xeloda + Temodar
82	Temodar + Lapatinib
83	Cytoxan + Carboplatinum
84	Navelbine + Temodar
85	Xeloda + Lapatinib
86	Navelbine + Xeloda + Lapatinib
87	Navelbine + Xeloda + Doxil
88	Navelbine + Xeloda + Taxotere + Carbo
89	Cytoxan + Methotrexate
90	Taxotere + Abraxane
91	Taxol + Sutent
92	Xeloda + Taxotere + Gemzar
93	Ifex
94	Etoposide
95	Mitoxantrone+ Ixempra + Ifex
96	Mitoxantrone+ Ifex
97	Gemzar+ Lapatinib
98	ABT 888
99	Panobinostat
100	Doxil+ Abraxane
101	Cytoxan + Taxotere
102	5-FU + Methotrexate
103	Xeloda + Sutent
104	Abraxane + Ixempra
105	Taxotere + Epirubicin + Melphalan
106	Navelbine + Carboplatinum
107	Gemzar+Adriamycin
108	Xeloda+ Ixempra
109	Xeloda + Adriamycin
110	Doxil + Adriamycin
111	Gemzar + Xeloda + Lapatinib
112	Iniparib (BSI-201)
113	Carbo + Taxol + ABT 888

10	Erythropoietin, Procrit, Aranesp
11	Neulasta, Neupogan
12	Surgery
13	Avastin vs. Placebo (Ribbon trials)
14	Known Avastin
15	Denosumab vs. Placebo
16	Zometa vs. Placebo
17	Temodar
18	Chlodronate vs placebo B-34
19	AMG 479 study
20	Rituxan
21	Dasatinib vs. Placebo (UPCI # 08-156)
22	Clodronate (UPCI # 06-031)

D.2 MBC STUDY CODING SHEET (CHEMO THERAPY)

Table 39. Chemotherapy drugs classified by chemotherapy type

ChemoWordIndex																			
Word	Chemo Type	Cyclophosphamide	Platinum	5FU	Methotrexate	Doxorubicin	Taxanes	Gemcitabine	Vinorelbine	Lapatinib	Epitholone	Mitoxantrone	Sunitinib	Temozolomide	FolinicAcid	GrowthFactor	Irinotecan	Ispinesib	Unknown
Cytoxan	1	X																	
Carbo	2		X																
Carboplatinum	2		X																
Cisplatin	2		X																
Xeloda	3			X															
Xeloda ==> deleted (same as 45)	3			X															
5-FU	3			X															
Methotrexate	4				X														
Adriamycin	5					X													
Doxil	5					X													
Epirubicin	5					X													
Adriamycine	5					X													
Taxol	6						X												
Taxotere	6						X												
Abraxane	6						X												
deleted (same as 30, Abraxane)	6						X												
Gemzar	7							X											
Navelbine	8								X										
Navalbene	8								X										
Lapatinib (Tykerb)	9									X									
Lapatinib	9									X									
Epitholone	10										X								
Epitholone B	10										X								
Lxabepilone (Ixempra)	10										X								
Mitox	11											X							
Mitoxantrone	11											X							
Sutent	12												X						
Temodar	13													X					
Leukovorin	14														X				
Veg F	15															X			
Veg F.	15															X			
CPT-11	16																X		
SB-715992	17																	X	
Lapatinib vs. Placebo and Xeloda																			
Triapine																			
Lapatinib vs. Placebo																			

D.3 MBC STUDY CODING SHEET (HORMONAL THERAPY)

Table 40. Hormonal drugs classified by hormone type

HormoneUniqueWords							
Word	**GenericName**	**HormoneType**	**AromataseInhibitor**	**SERM**	**ERAntagonist**	**GnRHAnalogue**	**Progestin**
Femera	letrozole	1	X				
Femara	letrozole	1	X				
Aromasin	eremestane	1	X				
Arimidex	anastrozole	1	X				
Arimadex	anastrozole	1	X				
Tamoxifen	tamoxifen	2		X			
Raloxifine	raloxifene	2		X			
Fareston	toremifene citrate	2		X			
TAS-108	TAS-108	3			X		
Fulvestrant	fulvestrant	3			X		
Faslodex	fulvestrant	3			X		
Zoladex	goserelin	4				X	
Lupron	leuprolide	4				X	
Megace	megestrol acetate	5					X

D.4 MBC STUDY CODING SHEET (METASTATIC LOCATION)

Table 41. Metastatic locations categorized into eight groups

MetastaticSiteWordIndex									
Word	**MetSiteType**	**Brain**	**Bone**	**Lung**	**Liver**	**AdrenalGland**	**SoftTissue**	**Other**	**LymphNode**
CSF	1	X							
Meningeal carcinomatosis	1	X							
Pituitary	1	X							
Brain	1	X							
CNS	1	X							
Leptomeningeal	1	X							
Leptomenigeal	1	X							
Dura	1	X							
Sternum	2		X						
Bone	2		X						
Scalp	2		X						
Bone marrow	2		X						
Orbital	2		X						
Pelvis	2		X						
Orbit	2		X						
Rib	2		X						
Thorax	3			X					
Lung	3			X					
Liver	4				X				
Adrenal gland	5					X			
Adrenal	5					X			
Neck	6						X		
Omentum	6						X		
Mediastinum	6						X		
Brachiplexy	6						X		
Brachial plexus	6						X		
Chest Wall	6						X		
Abd wall	6						X		
Abdominal	6						X		
Pleura	6						X		
Pleura Only	6						X		
Skin	6						X		
Pluera	6						X		
Peritoneum	6						X		
Sking	6						X		
Soft tissue	6						X		
Skeletal muscle	6						X		
Small bowel	7							X	

Table 41 (Continued)

MetastaticSiteWordIndex									
Word	MetSiteType	Brain	Bone	Lung	Liver	AdrenalGland	SoftTissue	Other	LymphNode
Colon	7							X	
Malignant pericardial effusion	7							X	
Spleen	7							X	
Thymus	7							X	
Appendix	7							X	
Kidney	7							X	
Abdomen	7							X	
Endometrial	7							X	
Esophageal	7							X	
Fallopian tube	7							X	
Gall bladder	7							X	
Stomach	7							X	
Bladder	7							X	
Pericardium	7							X	
Bladder mucosa	7							X	
Gastric	7							X	
Pancreas	7							X	
Ovary	7							X	
Retinal	7							X	
Parotid	7							X	
Mesentary	7							X	
Uterus	7							X	
Renal	7							X	
Axillary	8								X
Cervical	8								X
Cervical node	8								X
Axilla	8								X
Cervical In	8								X
Cervical L/N	8								X
Meidastinal L/N	8								X
Occipital L/N	8								X
Thyroid	8								X
Suprahilar	8								X
Sq nodes	8								X
Shoulder nodes	8								X
SC nodes	8								X
Retroperitoneum	8								X
Retroperitoneal	8								X
retroperital	8								X
Prevascular	8								X
Peritoneal L/N	8								X
Peritoneal	8								X
Pericardial/Periaortic nodes	8								X
Mediatinal L/N	8								X
Omental nodes	8								X
Groin	8								X
Mesenteric nodes	8								X

Table 41 (Continued)

MetastaticSiteWordIndex									
Word	**MetSiteType**	**Brain**	**Bone**	**Lung**	**Liver**	**AdrenalGland**	**SoftTissue**	**Other**	**LymphNode**
Mesenteric	8								X
Medistinal L/N	8								X
Mediastinal nodes	8								X
Mediastinal node	8								X
Mediastinal L/N	8								X
Mediastinal	8								X
Inguinal node	8								X
Iliac L/N	8								X
Hilar nodes	8								X
Hilar L/N	8								X
Hilar	8								X
Groin Nodes	8								X
Periaortic	8								X

D.5 PROTOCOL FOR MEDICAL ABSTRACTION PROCEDURE FOR SECONDAY REVIEW

Table 42. Treatment delay variable abstraction from medical records

Predictor Variable	Variables	Record	Others
Treatment delay	**DOM**	Date of metastatic breast cancer	*Date of CT scan or biopsy, when metastatic breast cancer was diagnosed. *If more than two different sites have different dates of metastasis, choose earlier date for DOM. If the earliest date and month of multiple metastases is not available, then choose the second earlier date of metastasis for DOM. *If the exact date for a certain month is not for sure, choose the first day for a date of DOM (ex., June 1). *When date of CT or biopsy for metastases was prior to date of initial breast cancer diagnosis, choose date of initial breast cancer diagnosis (Rationale: DOM prior to date of initial cancer diagnosis does not make sense). *If there were no medical records to verify DOM (month & date), follow the abstraction sheet.
	DOFT	Date of first treatment	*Date of first treatment including treatment type 2 through 19 *Missing of DOFT (i.e., patients did not have treatment until death or study end point) is coded as -1. *If the exact date for a certain month is not for sure, choose the first day for a date of DOM (ex., June 1). *If the exact date for DOFT is not for sure, assuming that the date is surely not the first day but around certain dates (ex., June 20~ July 7), choose the first date of the next month (ex., July 1) (Rationale: Choose the late month with the first day). *If there was no medical records to verify DOFT (month & date), follow the abstraction sheet.
	Treatment Delay	Treatment delay	*Treatment delay = Obs day
	Missing Day	Missing interval between DOM and DOFT	*Tx1wait_loss to_fu was coded as 1. *Tx_ was coded as -1. *If there is no information on the chart, follow the information on the abstraction sheet.
	Obs Day	Observation interval between DOM and DOFT	*Tx_ was coded as 1. *If there is no information on the chart, follow the information on the abstraction sheet.

Table 43. Metastatic location variable abstraction from medical records

Covariates	Variables	Coding and Record		Others
Metastatic sites	**MetSite**	>1		*Number of metastatic sites at metastatic breast cancer diagnosis
Metastatic location	**MetLoc**	1	Brain	*Location of metastasis at metastatic breast cancer diagnosis *MetSite,MetLoc within one month of metastasis diagnosis is included.
		2	Bone	
		3	Lung	
		4	Liver	
		5	Adrenal gland	
		6	Soft tissue	
		7	Other	
		8	Lymph node	

Table 44. Independent variables abstraction from medical records

Covariates	Variables	Coding and Record		Others
Marital status	**Marital Status**	0	No	*Current marital status (Information within a week before and after the date of metastasis could be used) at metastatic breast cancer diagnosis (0 includes single, divorced, widow etc.) * Data based on New patient assessment form (Yellow sheet, 1.3) or progress note * Nurse in clinic will give the information for missing data of marital status.
		1	Yes	
		-1	Unknown	
SES	**Insurance**	1	Private	*Data based on insurance record or progress note *Multiple insurances (e.g., 1+2) are possible. Patients who were aged 65 and over will be coded as 2.
		2	Medicare	
		3	Medicaid	
		4	No insurance	
		-1	Unknown	
	Education	1	< High school	Data based on New patient assessment form (Yellow sheet, 6.7)
		2	High school	
		3	> High school	
		-1	Unknown	
	Zip Code	Zip code		*-1: Unknown *To link income data with census block group *Data based on New patient assessment form (Yellow sheet) or insurance record *Information within a week before and after the date of metastasis could be used
BMI Stage I and BMI Stage II		-1:Unknown		
BMI Stage I :BMI at diagnosis of breast cancer	**Stage I Height**	Height (meters)		*Use NHLBI(NIH) calculator *Data based on out patient flow sheet *Data before, after 1 month of diagnosis could be used.
	Stage I Weight	Weight(kilograms)		
	Stage I BMI	Weight/Height^2		
BMI Stage II :BMI at diagnosis of metastatic breast cancer	**Stage II Height**	Height (meters)		*Use NHLBI(NIH) calculator *Data based on out patient flow sheet *Data before, after 1 month of metastasis could be used.
	Stage II Weight	Weight(kilograms)		
	Stage II BMI	Weight/Height^2		
Weight change between stage I and stage II	**Weight Change**	Weight (stage I) – Weight (stage II)		Blank: Unknown, and when MoMet is 0
Menopausal state	**Menopause**	0	No	*Post menopause includes an artificial menopausal status (ex., total, radical hysterectomy). *When patients underwent Lupron, their menstrual status is at pre menopausal status. *Data based on Yellow sheet (2.2) or progress note or information from Dr. Peg for missing data
		1	Yes	
		-1	Unknown	

Table 44 (Continued)				
Covariates	Variables	Coding and Record		Others
Comorbidity	**Charlson_Index**	Score 0-31		*Data based on Yellow sheet (2.1, 2.5, 3), progress note, and correspondence with laboratory results *Use access file to calculate Charlson's score adjusted for age. *Age-adjusted score are used (aim1, and aim2). *Do not enter "metastatic solid tumor" weighted as 6.
	Charlson_ Descriptive	Charlson_ Comorbidity lists		
	Hypertension	0	No	Data based on Yellow sheet (2.1, 3), MedicationReconciliationForm (Red sheet); OutpatientFlowSheet; progress note, and correspondence
		1	Yes	
		-1	Unknown	
	AbstractionDate	Date for Assessing comorbid conditions.		-1: Unknown
	FirstvisitDate	Date when the patient first visited at Magee corresponding to the date written in Yellow sheet.		-1: Unknown
	Noofvisitfor7mo	Frequency of patient-visits during 7 months (before 6 months and after 1 month of metastasis) if patient visited before the metastasis.		-1: patient came on the same month when she was diagnosed with the metastasis or patient came after the metastasis or unknown.
	NoofComorbidity	The number of comorbid conditions listed in Yellow sheet (2.1)		-1: patient did not have Yellow sheet.

Table 45. Weighted index of Charlson comorbid conditions

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

➔ See Appendix of Charlson M.E. et al, 1987[58] and Deyo R.A. et al, 1992[105].
➔ Follow the Charlson's index-criteria[58] if there is a discrepancy between Charlson's and Deyo's criteria.

Specific criteria for selective charlson comorbid conditions

➔ *Myocardial infarction* does not include patients with coronary artery disease (CAD) without myocardial infarction (ICD-9-CM: 429.89).

➔ *Congestive heart failure* includes patients with medication. It dose not include more severe cases: patients who are on medication, but have had no symptomatic response and no evidence of improvement of physical signs. [58] These cases are not supposed to be cared in hospital because of illness-severity. Thus, all patients with medication for congestive heart failure in hospital are considered as having congestive heart failure scored 1.

➔ *Dementia* includes Alzheimer's disease (ICD-9-CM: 294.1) even if Alzheimer's disease was not counted as the Charlson comorbidity index components in Deyo R.A. et al, 1992.

➔ *Chronic pulmonary disease* includes mild, moderate, severe pulmonary disease: Bronchitis, Emphysema, Asthma, Bronchiectasis, Extrinsic allergic alveolitis, Chronic airway obstruction not elsewhere classified, Pneumoconioses, and Chronic respiratory condition due to fumes and vapors. Pulmonary embolism (ICD-9-CM: 415.1) and pulmonary hypertension (ICD-9-CM: 416.8) will not be included in Charlson_Index and Charlson_Descriptive variables.

➔ *Connective tissue disease* indicates rheumatologic disease. Among rheumatologic diseases, moderate to severe rheumatoid arthritis are coded when the patients got treatment of rheumatoid arthritis with the corresponding ICD-9-CM codes according to Deyo et al. [105]

➔ *Mild liver disease* includes chronic hepatitis:
Hepatitis exposure history in the yellow sheet (2.5) will be considered as chronic hepatitis if there is no further information such as hepatitis-antibody and antigen results regardless of their liver function tests and regardless of the date written on Yellow sheet. Few patients (less than 10% of patients with chronic hepatitis) get the antibody after chronic hepatitis, which are regarded to be cured.

➔ *Diabetes* with end organ damage (score 2) includes only severe diabetes. Moderate and mild diabetes are scored as 1 with patients having previous hospitalizations for ketoacidosis, hyperosmolar coma, or control and those with juvenile onset or brittle diabetics (moderate diabetes), and all other diabetes treated with insulin or oral hypoglycemia (mild diabetes), but not diet alone.

➔ *Moderate or severe renal disease* includes patients on dialysis, those who had a transplant, those with uremia (severe renal disease), and patients with serum creatinines of >3 mg% (moderate renal disease). Mild renal disease with serum creatinines of 2-3 mg% will not be included in Charlson_Index and Charlson_Descriptive variables even if Deyo R.A. et al counted the mild renal disease as the Charlson comorbidity index components.

D.6 REPRODUCIBILITY STUDY OF CHARTS ABSTRACTION PROCEDURE WITH CHARLSON COMORBIDITY AND HYPERTENSION

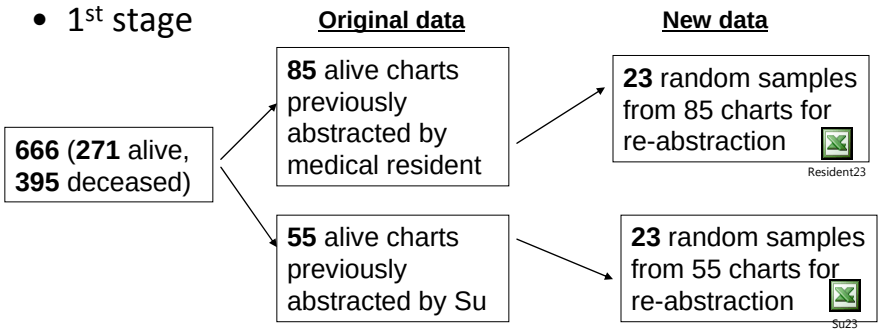
Overview

1. Select a random sample of n=23 charts previously abstracted by Su.
2. Select a random sample of n=23 charts previously abstracted by medical resident.
3. Re-abstract n=46 charts for the data elements comprising comorbidity index at the time of breast cancer metastasis.
4. Arrange entry of results from both the initial and repeat chart abstractions into an electronic database.
5. Analyze for each data element of comorbidity index, with standard measures of inter / intra-observer reliability.

Figure 29. Overview for the process of inter or intra observer reliability study

Data Arrangement

- 1st stage



- 2nd stage: combined original data with new data by using SAS

Figure 30. Data arrangement of original and new data

Inter-Observer (Between-Observer) Reliability: Charlson_Index

Frequency		Charlson_Index_II (Repeated)						
		0	1	2	4	5	7	Total
Charlson_Index_I (Original)	0	16	0	0	0	1	0	17
	1	0	1	0	0	0	0	1
	2	0	0	1	0	0	0	1
	4	0	0	0	2	0	0	2
	5	0	0	0	0	1	0	1
	7	0	0	0	0	0	1	1
Total		16	1	1	2	2	1	23

- Weighted Kappa Coefficient: **0.8767**
- **P <.0001** with two sided test
- Discrepancy due to mild liver disease (ex., chronic hepatitis)

Figure 31. Inter observer reliability study with Charlson index variable

Table: Weighted index of comorbidity		
Assigned weighted for diseases	Conditions	
1	Myocardial infact	1
	Congestive heart failure	2
	Peripheral vascular disease	3
	Cerebro-vascular disease	4
	Dementia	5
	Chronic pulmonary disease	6
	Connective tissue disease	7
	Ulcer disease	8
	Mild liver disease	9
	Diabetes	10
2	Hemiplegia	11
	Moderate or severe renal disease	12
	Diabetes with end organ damage	13
	Any tumor	14
	Leukemia	15
	Lymphoma	16
3	Moderate or severe liver disease	17
6	Metastatic solid tumor	18
	AIDS	19

Inter-Observer (Between-Observer) Reliability : Charlson_Descriptive

Charlson_Descriptive Frequency		
Codes for conditions	**Original**	**Repeated**
0 (no co-morbidity)	17	16
1	1	1
2	1	1
7	1	1
9	1	2
10	1	1
12	1	1
14	3	3
Total	**26**	**26**

Figure 32. Inter observer reliability study with Charlson descriptive variable

Inter-Observer (Between-Observer) Reliability: Hypertension

Frequency		**Hypertension_II (Repeated)**			
		-1	**0**	**1**	**Total**
Hypertension_I (original)	**-1**	2	0	0	**2**
	0	0	11	0	**11**
	1	1	0	9	**10**
Total		**3**	**11**	**9**	**23**

- Kappa Coefficient: **0.9263**
- **P <.0001** with two sided test

Figure 33. Inter observer reliability study with hypertension variable

Intra-Observer (Within-Observer) Reliability: Charlson_Index

Frequency		Charlson_Index_II (Repeated)						
		0	1	2	3	4	5	Total
Charlson_Index_I (Original)	0	17	0	0	0	0	0	17
	1	0	1	0	0	0	0	1
	2	0	0	2	0	0	0	2
	3	1	0	0	0	0	0	1
	4	0	0	0	0	1	0	1
	5	0	0	0	0	0	1	1
Total		18	1	2	0	1	1	23

- Weighted Kappa Coefficient: **0.8832**
- P **<.0001** with two sided test
- Discrepancy due to Tumor (ex., skin cancer)

Figure 34. Intra observer reliability study with Charlson index variable

Table: Weighted index of comorbidity		
Assigned weighted for diseases	Conditions	
1	Myocardial infact	1
	Congestive heart failure	2
	Peripheral vascular disease	3
	Cerebro-vascular disease	4
	Dementia	5
	Chronic pulmonary disease	6
	Connective tissue disease	7
	Ulcer disease	8
	Mild liver disease	9
	Diabetes	10
2	Hemiplegia	11
	Moderate or severe renal disease	12
	Diabetes with end organ damage	13
	Any tumor	14
	Leukemia	15
	Lymphoma	16
3	Moderate or severe liver disease	17
6	Metastatic solid tumor	18
	AIDS	19

Intra-Observer (Within-Observer) Reliability : Charlson_Descriptive

Charlson_Descriptive Frequency		
Codes for conditions	**Original**	**Repeated**
0 (no co-morbidity)	17	18
1	1	1
5	1	1
6	2	2
9	1	1
14	1	0
Total	**23**	**23**

Figure 35. Intra observer reliability study with Charlson descriptive variable

Intra-Observer (Within-Observer) Reliability: Hypertension

Frequency		Hypertension_II (Repeated)			
		-1	0	1	Total
Hypertension_I (original)	-1	2	0	0	2
	0	0	15	0	15
	1	0	0	6	6
Total		2	15	6	23

- Kappa Coefficient: **1.0000**
- **P <.0001** with two sided test

Figure 36. Intra observer reliability study with hypertension variable

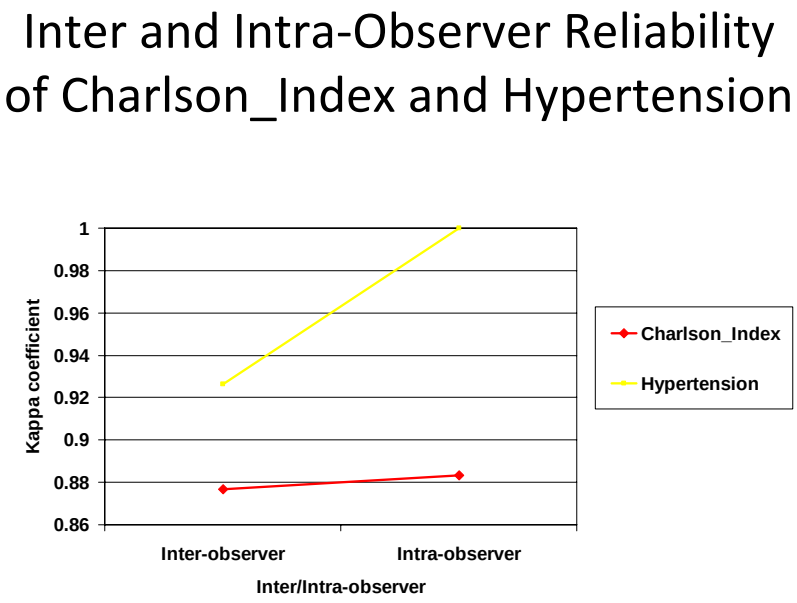


Figure 37. Graph for kappa coefficients of inter and intra observer reliability study for Charlson index, and hypertension

D.7 MISSING DATA

Table 46. Report of missing data

Missing data report

	Chart not available N=114		Chart available N=557	
	N	%	N	%
Abstracted by Su Yon Jung				
Marital status	114	100%	223	40%
Insurance	114	100%	245	44%
Education	114	100%	71	13%
Zip code	114	100%	196	35%
BMI breast cancer diagnosis	114	100%	293	53%
Entry BMI	114	100%	114	20%
Weight change	114	100%	358	64%
Menopause	114	100%	59	11%
Charlson Index	114	100%	6	1%
Hypertension	114	100%	28	5%
Abstracted by study nurses				
Number of metastatic sites	7	6%	0	0%
Metastatic locations	7	6%	0	0%
Age	0	0%	0	0%
Race	0	0%	0	0%
ER	5	4%	4	1%
HER2	20	18%	41	7%

Table 47. Assessment of relationship between missing and other missing variables; between missing and complete variables

Missing variables												Complete Variables				
	Marital Status	Insurance	Education	Zip code	StageI BMI	StageII BMI	Weight-change	Meno-pause	Charlson_Index	Hyper-tension	HER2	ER	Metsite	Metloc	Age	Race
Operating- system	*SPSS*	*SAS*	*SAS*	*SPSS*	*SPSS*	*SPSS*	*SPSS*	*SAS*	*SPSS*	*SAS*	*SAS*	*SAS*	*SPSS*	*SAS*	*SPSS*	*SAS*
Marital status	N/A	P=<.00	P=<.00	P=.83	P=.46	P=.03	P=.40	P=<.00	P=.66	P=<.00	P=.01	P=.01	P=.48	P=.17	P=.26	P=.85
Insurance	N/A	N/A	P=<.00	P=.03	P=.12	P=.23	P=.10	P=<.00	P=.00	P=<.00	P=.15	P=.02	P=.16	P=.30	P=.00	P=.94
Education	N/A	N/A	N/A	P=.00	P=.11	P=.97	P=.73	P=<.00	P=.01	P=<.00	P=<.00	P=.03	P=.16	P=.03	P=.09	P=.05
Obs values of Gths vs. Obs values of complete variables (Age, Black)															P=<.00	Black: P=.75
Zipcode	N/A	N/A	N/A	N/A	P=.89* P=.10** *SAS,* P=<.00	P=.38* P=.06** *SAS,* P=<.00	P=.91* P=.04** *SAS,* P=<.00	*SPSS,* P=.99	P=.58* P=N/A** *SAS,* P=<.00	*SPSS,* P=.00	*SPSS,* P=.00	P=.00	P=.065	P=.02	P=.01	P=.70
Income	P=.23	*SPSS,* P=.82	*SPSS,* P=.99	N/A	P=.99* P=.52** *SAS,* P=<.00	P=.40* P=.98** *SAS,* P=<.00	P=.67* P=.84** *SAS,* P=<.00	*SPSS,* P=.54	P=.59* P=N/A** *SAS,* P=<.00	*SPSS,* P=.42	P=<.00	P=.00	P=.07	P=.02	P=.01	P=.70 Black: P=.61
Obs values of Income vs. Obs values of complete variables (Age, Black)															P=.18	Black: P=<.00
StageIBMI	N/A	N/A	N/A	N/A	N/A	P=.60* P=.31** *SAS,* P=<.00	P=.79* P=.65** *SAS,* P=<.00	*SPSS,* P=.21	P=.15* P=N/A** *SAS,* P=<.00	*SPSS,* P=.25	*SPSS,* P=.61	P=.41	P=.43	P=.15	P=.90	P=.80
StageIIBMI	N/A	N/A	N/A	N/A	N/A	N/A	P=.85* P=.70** *SAS,* P=<.00	*SPSS,* P=.32	P=.65* P=.78** *SAS,* P=<.00	*SPSS,* P=.19	*SPSS,* P=.87	P=.00	P=.19	P=.04	P=.00	P=.51
Obs values of StageIIBMI vs. Obs values of complete variables (Age, Black)															P=.04	Black: P=.05
Weight change	N/A	N/A	N/A	N/A	N/A	N/A	N/A	*SPSS,* P=.73	P=.98* P=N/A** *SAS,* P=<.00	*SPSS,* P=.42	*SPSS,* P=.43	P=.08	P=.57	P=.36	P=.48	P=.91
Menopause	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	P=.00	P=<.00	P=.03	P=.00	P=.30	P=.01	P=.00	P=.74
Obs values of Menopause vs. Obs values of complete variables (Age, Black)															P=<.00	Black: P=.26
Charlson_ Index	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	*SPSS,* P=.66	*SPSS,* P=.085	P=<.00	P=.28	P=.015	P=.00	P=.72
Hypertension	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	P=.02	P=.00	P=.07	P=.12	P=.00	P=.35
HER2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	P=<.00	P=.16	P=.03	P=.00	P=.72

* Relationship of Missing vs. Present of right variables in terms of Present of 1st row variables.

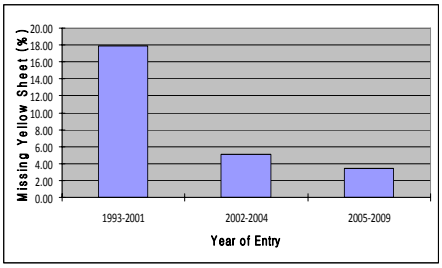
** Relationship of Missing vs. Present of 1st row variables in terms of Present of right variables.

Table 48. Analytic methods for the relationship between missing and other missing variable, or between missing and complete variable using SAS and SPSS

Variable Type I	Missing Data I	Case	Operating System	How to compare		Missing Data II	Variable Type II
Category Variables	**Complete variable**	Case 1	*SAS, Chisq test*	Each categories	Missing-freq Present-freq	**Missing variable**	**Category Variable**
	Missing variable	Case 2	*SAS, Chisq test*	Missing-freq Present-freq	Missing-freq Present-freq	**Missing variable**	
Category Variables	**Missing variable**	Case 1	*SPSS, Ttest*	Missing Present	means	**Complete variable**	**Continuous Variables**
	Missing variable	Case 2	*SPSS, Ttest*	Missing Present	Present-means	**Missing variable**	
	Complete variable	Case 3	*SAS, Chisq test*	Each categories	Missing -freq Present -freq	**Missing variable**	
Continuous Variables	**Complete variable**	Case 1	*SPSS, Ttest*	Means	Missing Present	**Missing variable**	**Continuous Variables**
	Missing variable	Case 2	*SPSS, Ttest*	Present-means	Missing Present	**Missing variable**	
				Missing Present	Present-means		
			SAS, Chisq test	Missing-freq Present-freq	Missing-freq Present-freq		

	Entry Year (P<0.001)			
Yellow sheet	1993-2001	2002-2004	2005-2009	**Total**
Unavailable, n	30	9	7	**46**
Available, n	138	170	199	**507**
Unavailable, %	*18*	*5*	*3*	***8***
Total	***168***	***179***	***206***	***553***

	Entry Year (*P=.45)*			
Co-morbidities	1993-2001	2002-2004	2005-2009	**Total**
0, n	19	17	28	**64**
≥1, n	119	153	171	**443**
≥1, %	*86*	*90*	*86*	***87***
Total, n	***138***	***170***	***199***	***507***



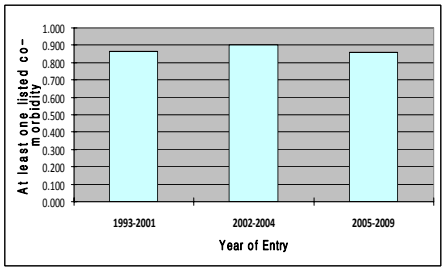
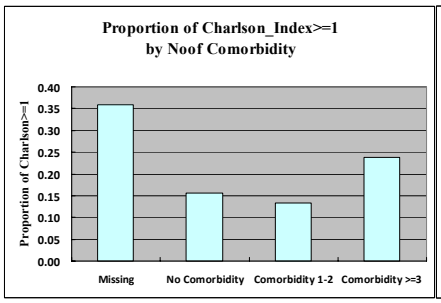


Figure 38. Number of co-morbidities listed on "Yellow Sheet", by Year of Entry

	Co-morbidities				
Charlson Index	Missing, n	0, n	1-2, n	>=3, n	***Total***
Missing, n	1	0	1	4	***6***
0, n	31	54	168	185	***438***
>=1	18	10	26	59	***113***
>=1, %	*36*	*16*	*13*	*24*	***20***
0, %	*62*	*84*	*86*	*75*	***79***
Total	***50***	***64***	***195***	***248***	***557***



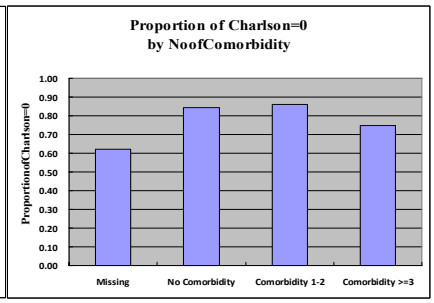


Figure 39. Charlson co-morbidity Index by number of co-morbidities on "Yellow-Sheet"

	Abstraction date				
Charlson Index	Missing	Jul_Aug2009	Nov_Dec2009	Jan-Apr2010	***Total***
Missing	1	1	0	4	***6***
0	0	113	99	226	***438***
>=1	0	25	22	66	***113***
>=1, proportion	*0*	*0.180*	*0.182*	*0.223*	***0.203***
Total	***1***	***139***	***121***	***296***	***557***

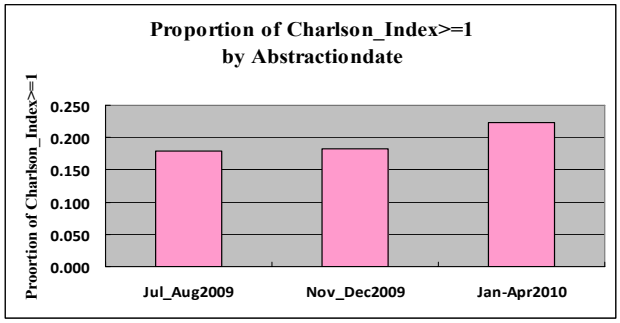


Figure 40. Charlson co-morbidity Index according to abstraction date

Status=0, Alive	**Abstractiondate**				
Charlson Index	Missing	Jul_Aug2009	Nov_Dec2009	Jan-Apr2010	***Total***
Missing	1	1	0	2	***4***
0	0	113	80	18	***211***
>=1	0	25	21	8	***54***
>=1, proportion	*0*	*0.180*	*0.208*	*0.286*	***0.201***
Total	***1***	***139***	***101***	***28***	***269***

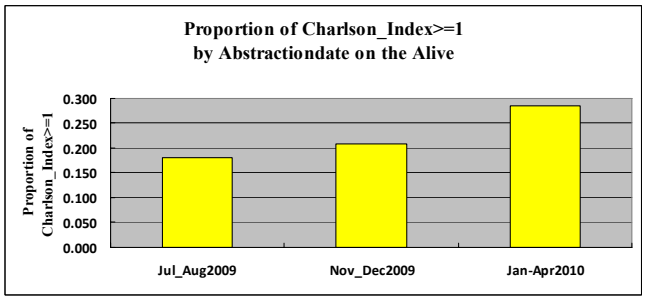


Figure 41. Charlson co-morbidity Index according to abstraction date by status (=0, Alive)

Status=1, Deceasd	Abstractiondate				
Charlson Index	Missing	Jul_Aug2009	Nov_Dec2009	Jan-Apr2010	***Total***
Missing	0	0	0	2	***2***
0	0	0	19	208	***227***
>=1	0	0	1	58	***59***
>=1, proportion	*0*	*0*	*0.050*	*0.216*	***0.205***
Total	***0***	***0***	***20***	***268***	***288***

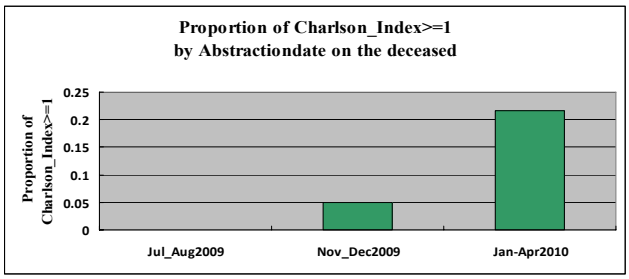
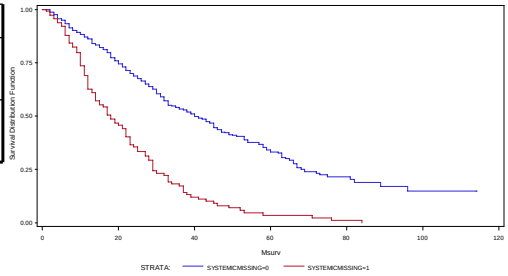


Figure 42. Charlson co-morbidity Index according to abstraction date by status (=1, Deceased)

Total = 671					
Variable	**Value**	**Censored, n**	**Failed, n**	**Med**	**Mean (SE)**
Msurv	**Month**	278	393	33.0	41.6 (1.39)



		Among SystemicMissing =114					Among NonSystemicMissing= 557				
Variable	**Value**	**Censored, n**	**Failed,n**	**Med**	**Mean (SE)**	**HR (P-value)**	**Censored, n**	**Failed,n**	**Med**	**Mean (SE)**	**HR (P-value)**
Msurv	**Month**	9	105	18.0	22.3 (1.63)	**2.79 (<.00)**	269	288	40.0	46.5 (1.625)	**1.00**

Figure 43. Follow-up time by Systemic Missing

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