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Survival Analysis of Breast Cancer Patients with Different Chronic Diseases Using Parametric and Semi-Parametric Approaches

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Abstract

Introduction: There is a lack of information on the extent of dependency between chronic diseases and the survival rate of breast cancer. Until date, none of the models proposed has determined the impact of chronic diseases on breast cancer survival. This study, therefore, aimed to investigate the impacts of chronic diseases such as diabetes, blood pressure, and endocrine disorders on the survival of breast cancer patients through a comprehensive research.

Methods: All (n = 1822) breast cancer patients treated in the three hospitals of Tehran from 2007 through mid–2016 were included in this study. A comprehensive study was conducted by focusing on the chronic disease data of the studied patients. The parametric and semi-parametric approaches, as well as non-parametric Kaplan-Meier analysis, were performed. This research proposes two models for analyzing breast cancer survival. A comparative analysis of the models was performed based on the Akaike criterion.

Results: Chronic diseases have been found to affect the survival of breast cancer patients. This research considered 436 individuals, among the patients with chronic diseases including hypertension, diabetes, hypo- and hyperthyroidism, and heart problems at the frequencies of 12.38%, 11.69%, 8.71%, and 8.02%, respectively. This study indicated that the 5-year survival of breast cancer patients with chronic diseases was 72% and that it was 82% for other breast cancer patients. The statistical analysis and the two proposed models revealed that chronic diseases significantly affect the survival of the study patients.

Conclusions: This comprehensive research evidence a significant difference in the survival rate of breast cancer patients with and without chronic diseases. The statistical analysis of the data indicated that chronic diseases can significantly affect the survival probability in breast cancer. Heart problems and the combination of chronic diseases have a major influence on the survival rate of breast cancer patients as compared to other cases.

INTRODUCTION

Breast cancer is the most common cancer occurring among Iranian women as well as in those from other countries. Similar to that in the Middle East countries, the mean age of breast cancer diseases in Iran is 10 years lower than that in the developed countries. Moreover, due to the lack of performing systematic screening, most of the patients are referred for treatment when cancer has reached advanced stages [1]. Breast cancer is increasingly regarded as a heterogeneous disease that can be classified into distinct molecular subtypes with prognostic significance [2]. Hence, survival analysis is considered to be an important issue for physicians. Several different studies have contributed to the survival rate of breast cancer. Atashgar et al. [3] reviewed different proposed models corresponding to the survival analysis of breast cancer patients. They identified 39 models for the survival analysis, determining risk factors for breast cancer. Metastasis [4, 6, 14, 16, 28, 42], background of benign tumors [4], and age at diagnosis [4, 5, 16,

22, 23,24, 25, 26, 28, 29, 32–37, 39] were considered as the main factors in the survival analysis. Some studies emphasized on the factors such as hormone therapy (hormone receptor) [9, 12, 16, 20, 22, 23, 25, 27, 33, 35, 36, 38], Her2 [9, 11], grade [9, 11, 13, 19, 21, 24, 31, 34, 37, 38], and lymph node involvement [11, 19, 20, 21, 23, 38, 39]; however,
others did not propose hormone therapy as a factor [10]. The proportion of lymph nodes [12, 24] and education [12] have also been studied in some models. Surgery [14, 15, 25, 29, 36] and CA 15–3 marker [15] are the other factors that can be considered in the survival analysis. Furthermore, the combination of the following factors have been suggested across different studies: familial history [24], smoking [24], affected side [20, 39], place of residence [29], number of involved lymph nodes [22, 24, 27, 31, 34, 35, 37], stage [5, 6, 8, 17, 25, 26, 42], stage of surgery [25], tumor size [16, 19, 20–24, 27, 28, 31, 34, 35, 37, 38, 41], complete clinical and pathological response [41], medicine [29], type of pathology [32], type of treatment [17, 21], chemotherapy [25, 33, 36, 37], neoadjuvant chemotherapy [18], radiotherapy [25, 33, 36], number of metastasis [30], bone pain [30], and time interval leading to bone metastasis [42]. No study has considered chronic diseases as an effective factor of survival analysis. In this study, the impacts of chronic diseases (i.e., diabetes, hypertension, and endocrine gland disorders like hypo- and hyperthyroidism) on the survival rates of breast cancer patients were examined through a comprehensive survey. Due to the relatively high rate of breast cancer in women and considering the importance of determining the survival rate after diagnosis and treatment of breast cancer, the impact of each chronic disease on the longevity and survival was investigated under two scenarios: 1) alone and 2) in combination with the diseases.

METHODS

In this study, a total of 1822 cancer patients with chronic diseases referred to three hospitals of Tehran (Besat, Bazarganan, and Chamran) between 2008 and 2017 were investigated. Of all the patients, 435 had a chronic disease type or a combination disease, 27 died, and the remaining patients were excluded. Data were analyzed by using two parametric and semi-parametric approaches. The literature indicates that, among the parametric models, the log-logistic approach is more applicable as compared to other parametric approaches. In this paper, besides semi-parametric approach of Cox proportion hazards, the parametric log-logistic was also used for the survival analysis of breast cancer patients in the case of the presence of chronic diseases. This analysis provided the survival rate of 1, 2, 3, 4, 5, 6, 7, 8, and 9-year-old patients with breast cancer in a perfect condition. The Kaplan-Meier curve was used for the statistical analysis of survival with or without chronic diseases to present a supplementary investigation. An Akaike criterion (AIC) was implemented for the comparative analysis of two parametric and semi-parametric survival models.

RESULTS

The analysis of all patient data demonstrated that 436 individuals had chronic diseases including diabetes, heart problems, endocrine glands disorders (i.e., hypo- and hyperthyroidism), hypertension, and other diseases (such as renal failure and asthma). Table 1 illustrates the distribution of different chronic diseases for the studied patients.

Table1. Various Chronic Diseases Associated with Cancer Patients

No	Type of Disease	No (%)
1	Hypertension	54 (12.38)
2	Diabetes	51 (11.69)
3	Hypo- and Hyperthyroidism	38 (8.71)
4	Heart Problems	35 (8.02)
5	Other Diseases	135 (30.96)
6	Combination of Chronic Disease	123 (28.21)

Table 2 indicates the effective parameters for the survival analysis of patients affected by breast cancer using the step-wise approach for parametric and semi-parametric approaches. As shown in Table 2, statistical analysis of the data obtained from the two proposed models revealed that chronic diseases significantly affected the survival of the studied groups of patients. The proposed models were designed using the stepwise method for the independent factors that affected the patients. As shown in Table 3, some factors were common across both semi-parametric Cox and parametric logistic log models. Table 3 shows the proposed model based on the data of Table 2.

Figure 1 addresses the Kaplan–Meier graph for breast cancer patients with and without chronic diseases. Figure 2 represents different Kaplan–Meier graphs with and without each chronic disease, separately for breast cancer patients. The Kaplan-Meier analysis (Figure 1) illustrates that the relative survival of breast cancer individuals with chronic diseases decreases gradually over a period of time. Figure 2 denotes that this difference is addressed relatively by individuals with heart problems and a combination of chronic diseases. Figure 1 indicates a significant difference in the 5th year of survival for cancer patients with chronic diseases ($p = 0.001$).

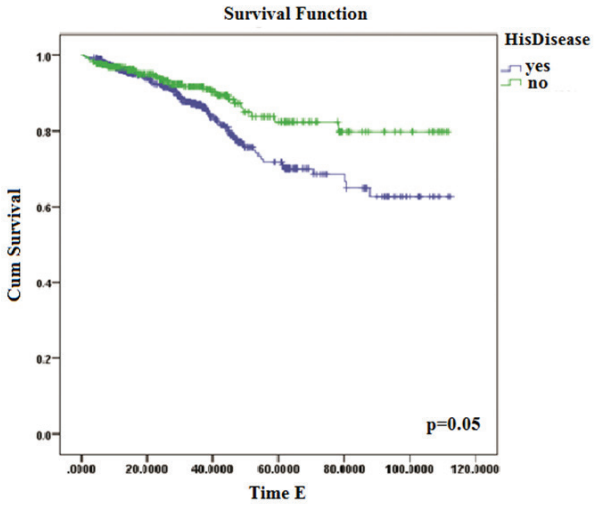

Figure 1: Curve Representing Breast Cancer Survival in the Conditions with and without Chronic Diseases. The vertical marks represent excluded patients. Exclusion indicates that the total survival time for the patient cannot be accurately determined.

DISCUSSION

Our results demonstrated a significant difference between the survival probability of breast cancer patients with and without chronic diseases, such that patients with chronic diseases have less chance to survive. Although several different researchers have proposed models for breast cancer survival, none have provided the considerable impact of chronic diseases on breast cancer patients' longevity. Some research such as Rasmusson and Shering [43, 44], Maruchi et al. [45], and Lemaire et al. [46] have asserted the existence of several breast cancer patients who had chronic diseases such as thyroid. This comprehensive research revealed that a breast cancer patient's longevity is directly affected by the condition of chronic diseases (such as diabetes, hypertension, and endocrine gland disorders such as hypo and hyper-thyroidism). We compared the survival analysis for two scenarios without and with chronic diseases for breast cancer patients. The result of the comparative analysis addressed the importance of the consideration for breast cancer patients with a chronic disease.

Both Cox and logistic log models addressed the impact of chronic diseases, and the Kaplan–Meier analysis illustrated that the chronic diseases affect breast cancer survival. The Akaike information criteria revealed that the Cox model fits better with the research data as compared to the log-logistic model. Therefore, Cox can be considered to be a more suitable approach for the analysis of breast cancer survival. The comparison of Kaplan–Meier graph in Figure 1 and the results listed in Table 2 (the row of chronic diseases history) indicate that Cox semi-parametric model is more capable of demonstrating the impact of chronic diseases on the longevity of breast cancer patients. Variables such as time of diagnosis, the background of chronic diseases, the number of involved lymph nodes, and metastasis addressed by both log-logistic and Cox models affected patients' survival.

This study indicates that the probabilities of survival for cancer patients with backgrounds of diabetes, hypo- and hyperthyroidism, hypertension, and other diseases without any chronic disease are nearly the same. On the other hand, the survival probability of cancer patients with heart problems or a combination of chronic diseases is less than those of other patients without those diseases. Notably, the analysis of the survival graph in Figure 2 revealed that, in some cases, the survival probability of patients without chronic diseases is less than that of those with them. This notion helped conclude that some patients were affected by a progressed type of cancer or by a developed metastasis. Hence, these two factors caused low longevity.

Our results thus indicated a significant difference between the survival probability of breast cancer patients with chronic diseases and those without these diseases.

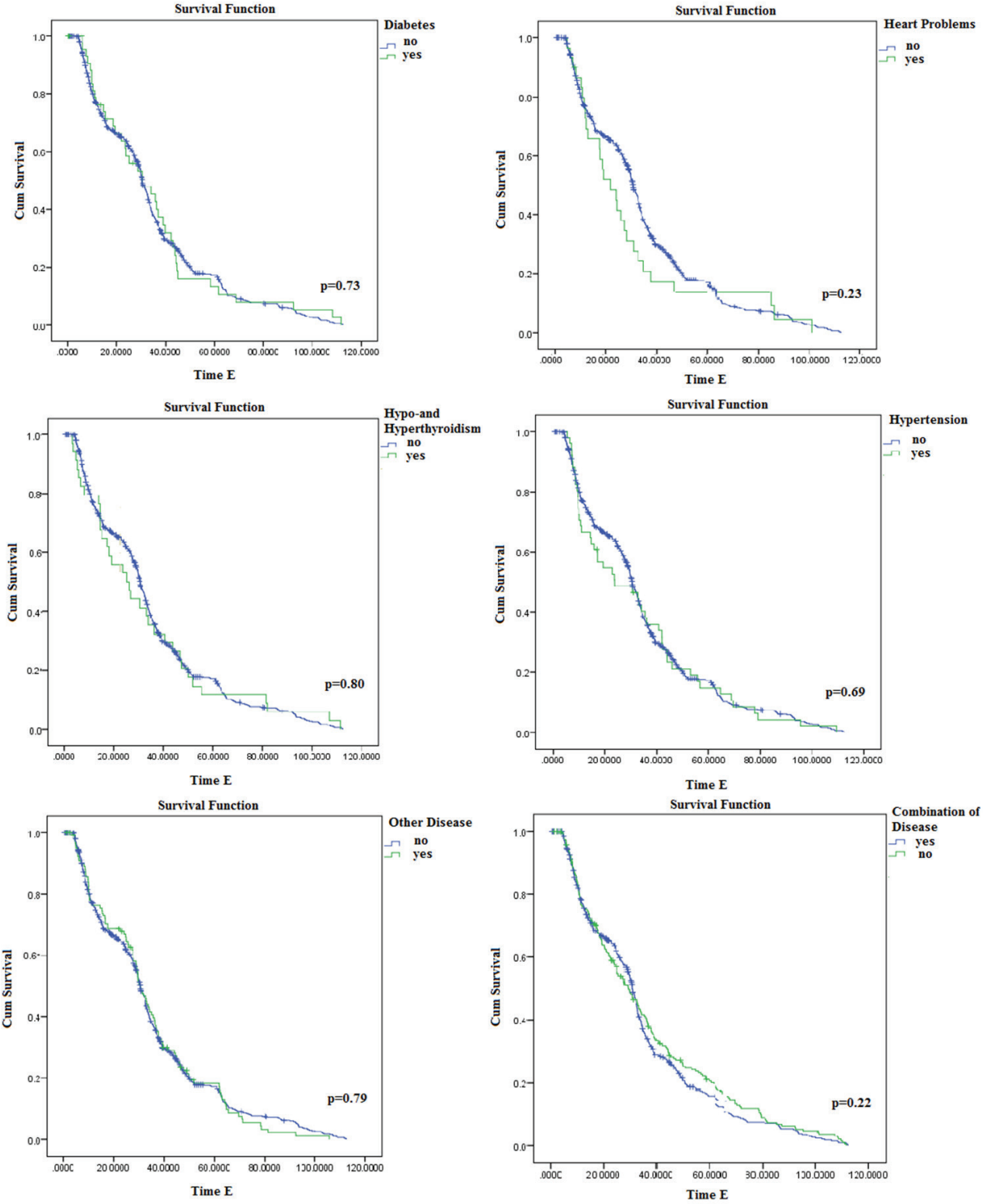

Figure 2: Comparison of Patients' Longevity Affected by Each of Chronic Diseases Vertical Tick Marks Represent Excluded Patients. Exclusion means the total survival time for that patient cannot be accurately determined.

Table2. Multivariate Analysis of Breast Cancer Survival

	LOG LOGISTIC				COX			
	Coefficient	Standard Deviation	Hazard Rate	P Value	Coefficient	Standard Deviation	Hazard Rate	P Value
Age	–0.036	0.009	0.964	000.0	0.066	0.015	1.069	000.0
Chronic Disease History	0.642	0.211	1.900	002.0	–1.219	0.353	296.0	0.001
Extracapsular Extension	–0.218	0.269	0.804	0.416	0.839	0.402	2.313	0.037
No. of Lymph Nodes	–0.020	0.018	0.980	0.245	0.115	0.045	122.1	0.011
Metastases	–0.857	0.458	0.424	0.061	1.299	0.652	3.665	0.046
Hormone Therapy	0.762	0.203	2.142	0.000	–2.398	1.272	091.0	0.059
Akaike		896.6				733.8		

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS APPROVAL

The ethics committee of Radiotherapy and Oncology Center of the Hospitals of Besaat & Bazarganan approved the study.

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