Multiple Imputation as a Means to Assess Mammographic vs. Ultrasound Technology in Determining Breast Cancer Recurrence

Göğüs Kanseri Nüksünü Belirlemede Mamografik Teknolojiye Karşı Ultrason Teknolojisini Değerlendirmek İçin Çoklu Değer Atama

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ABSTRACT Ultrasound and mammogram are two imaging tools used to determine breast cancer diagnosis. One prognostic factor measured by these technologies is tumor size and also can be used in the prediction of recurrence. Which technology offers better determination of diagnosis and gives better measurements of prognostic factors is an ongoing debate among clinicians. Examining the performance of these tools by the association between tumor size and recurrence could depend on the amount and nature of missing data, however. The purpose of this work is two-fold. The first purpose is to determine any relationship between recurrence and tumor size via ultrasound and mammogram by employing complete case analysis. The second purpose involves applying multiple imputation to determine the significance of any indicative associations found in the complete case analyses. In taking these approaches, we aim to show how multiple imputation can aid investigators in further understanding how to discern associations in their data relevant in clinical applications as predicting recurrence.

Key Words: Multiple imputation; mammography; ultrasound

ÖZET Ultrason ve mamografi göğüs kanseri tanısını belirlemede kullanılan iki görüntüleme aracıdır. Bu teknolojiler ile ölçülen prognostik bir faktör olan tümör boyutu, nüksün tahmininde de kullanılabilmektedir. Tanının belirlenmesinde hangi teknolojinin daha iyi olduğu ve hangi teknolojinin prognostik faktörlere ilişkin daha iyi ölçümler verdiği klinisyenler arasında devam eden bir tartışmadır. Tümör boyutu ve nüks arasındaki birliktelik ile bu araçların performanslarının incelenmesi kayıp verinin doğası ve miktarına bağlı olabilir.Bu çalışmanın amacı iki yönlüdür. İlk amaç tam durum analizini kullanarak ultrason ve mamogram ile tümör boyutu ve nüks arasındaki olası ilişkiyi belirlemektir. İkinci amaç, tam durum analizinde bulunan muhtemel belirleyici birlikteliklerin anlamlılığını belirlemek için çoklu değer atamanın uygulanmasını içermektedir. Bu yaklaşımlarla, çoklu değer atamanın araştırmacılara nüksü tahminleme gibi klinik uygulamalarla ilişkili verilerinde bulunan birlikteliklerin daha iyi anlaşılması için nasıl yardımcı olabileceğini göstermeyi amaçladık.

Anahtar Kelimeler: Çoklu değer atama; mamografi; ultrason

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One major debate in cancer research is which detection method or what prognostic factors offer(s) a superior approach in predicting recurrence. Tumor size as measured by ultrasound, mammogram, or magnetic resonance imaging (MRI) could further help clinicians in determining the likelihood of breast cancer recurrence. Results from these technologies could greatly vary, however; as tumors may be detected by ul-

trasound when mammogram data indicated a negative result. Different technologies could also give different measurements in tumor size. The work involves two objectives with respect to finding an ideal technology for predicting breast cancer recurrence. First, we tried to establish an association between tumor size and recurrence, and determine which technology used to measure size supported evidence for such an association. The significance of such an association could be affected by missing data. Our second objective was to determine how evidence of an association between size and recurrence could change after application of multiple imputation and how it assess its dependence on the variables involved in the imputation model. We focus on ultrasound, mammogram, and recurrence data from 302 patients treated at Northwestern Memorial Hospital, Chicago, IL, USA, from 1984 to 2010. After conducting complete case analyses, we applied a semi-parametric multiple imputation method to the data to see how these results change.

MAMMOGRAM VS. ULTRASOUND

The topic of whether mammogram or ultrasound is a better predictor of breast cancer has been explored previously. Leddy et al.[1] and Berg et al.[2] use receiver operating characteristic (ROC) analyses to show that ultrasound was able to detect solid tumors when mammogram results were negative. Berg et al.[2] also note that although MRI provided further improvement in detection, it may be less tolerable than ultrasound, making ultrasound a more suitable choice. With respect to the comparison between ultrasound and mammogram, Britton et al.[3] obtain results similar to the other studies involving ROC analyses, showing that ultrasound results are associated with increased sensitivity and only slightly lower specificity. These arguments give evidence to ultrasound as being an attractive alternative to mammogram in breast cancer diagnosis and assessing diagnostic measures such as size.

TUMOR SIZE AND RECURRENCE

The association between tumor size and recurrence is a controversial topic as different studies have found evidence for and against an association. While Wapnir et al.[4] did not find an association between tumor size and recurrence, they state that most tumor sizes in their population were small and not representative of a general population. Other studies as Dent et al.[5] present the relationship between tumor size and recurrence as being dependent on other factors. No evidence of an association was detected in cases negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor, although tumor size correlated with lymph node presence in both triple negative and other cases. Stronger associations between tumor size and recurrence were observed in Gasparini et al.,[6] Partridge et al.,[7] and Dowsett et al.,[8] both in univariate analyses and in multivariate analyses adjusting for other prognostic factors.

DATA

The data consist of 302 women whose records have been collected from the Northwestern Memorial Prentice Women's Hospital and who have been diagnosed with a new primary tumor between 1984 and 2010, and subsequently recurred in the same or other breast. Ages ranged from 20 to 93 years with a median of 49 years. Of 220 patients with available stage information, 82 (39.4%) were Stage II or III, 198 (80.8%) were Grade II or III, 141 (46.7%) were positive for estrogen receptor (ER), 94 (31.1%) were positive for progesterone receptor (PR), and 31 (10.3%) were positive for human epidermal growth factor receptor (Her2). We defined recurrence as opposed to no recurrence as any subsequent indication of cancer in the same breast. 71 (23.5%) of the patients had a recurrence. Table 1 and Figure 1 give the distribution for tumor size as measured by ultrasound and by mammogram for the entire population and by recurrence group.

STATISTICAL ANALYSIS

We first performed a statistical analysis on complete cases, comparing tumor size obtained via mammographic and ultrasound data via the Wilcoxon rank-sum test. The distribution of tumor size was summarized by recurrence group in terms of means, standard deviations, median, minima, and maxima.

TABLE 1: Summary statistics including missing data information for tumor size measured by ultrasound and mammogram for the entire patient population and by recurrence group.

	Variable	n	n missing	Mean	Std Dev	Median	25th Pctl	75th Pctl	Minimum	Maximum
All cases	Mammogram size	70	232	18.46	13.48	15.50	10.00	25.00	1.00	68.00
	Ultrasound Size	90	212	15.57	9.11	14.45	9.00	20.00	1.07	44.00
No Recurrence	Mammogram size	50	181	18.25	13.86	15.50	10.00	25.00	1.00	68.00
	Ultrasound Size	63	168	14.24	8.08	13.00	8.00	19.00	1.07	44.00
Recurrence	Mammogram size	20	51	18.98	12.80	16.00	9.50	26.00	3.00	50.00
	Ultrasound Size	27	44	18.66	10.67	15.00	9.90	27.00	1.30	39.00

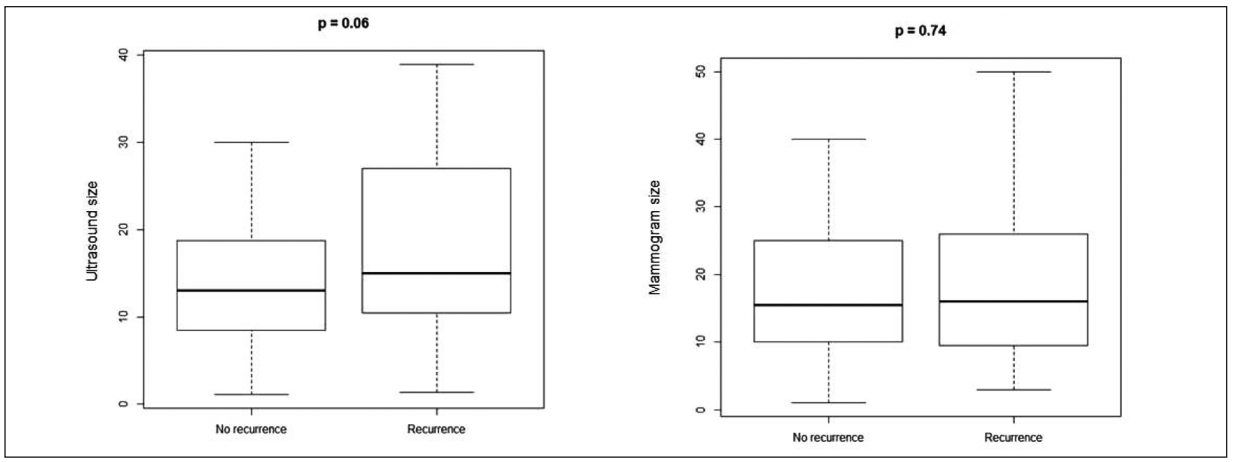

FIGURE 1: Distribution of ultrasound tumor size and mammogram tumor size by recurrence group presented by boxplots. Differences in ultrasound tumor size are marginally significant (p=0.06), whereas differences in mammogram tumor size are not significant (p=0.74).

Multiple imputation was applied to the data via a semi-parametric approach involving joint modeling framework further described below. Models considered to impute ultrasound data included the variables of ultrasound and recurrence data, ultrasound and mammogram data, and all three variables of ultrasound, recurrence, and mammogram data. The models including only ultrasound and mammogram data involved the semi-parametric approach for imputing continuous data as presented in Helenowski and Demirtas[9] and the other two models involved a semi-parametric approach for mixed continuous and binary data as given in Helenowski et al.[10] and Helenowski and Demirtas.[11] One thousand simulations were run, including ten imputations per simulation. The performance of the imputation methods were assessed via average estimates of pairwise correlations, standardized biases, root mean squared errors, coverage rates, and average widths of confidence intervals. Comparisons between recurrence groups of ultrasound tumor size were for each imputed data set were evaluated via the Wilcoxon rank-sum test and the distribution of the p-values obtained from the tests were summarized by means, standard deviations, median, minima, and maxima, and presented by histograms. Summary statistics for ultrasound tumor size by recurrence status were presented by boxplots.

SEMI-PARAMETRIC APPROACH TO MULTIPLE IMPUTATITON

We imputed our data semi-parametrically based on the techniques presented in Helenowski and Demirtas and Helenowski and Demirtas. In these methods, both continuous and binary variables are transformed to normally distributed values. Quantiles based on the standard normal distribution are derived for empirical cumulative distribution function (eCDF) values of the continuous data and nor-

mally distributed values corresponding to binary data are obtained via the methods described in Demirtas and Doganay.[12] Multiple imputation via joint modeling is then applied to the data sets with normally distributed entries and imputed values are back-transformed to the scale of the original data. For continuous variables, this procedure involves mapping the probability distribution function (PDF) values of the imputed data to the original scale using the method presented in Barton and Schruben[13] and dichotomizing the values by quantiles based on original probabilities for the binary data as in Equation (1).

$$\begin{aligned} &\Pr(Y_k = y_k \mid Y_1 = y_1, Y_2 = y_2, ..., Y_{k-1} = y_{k-1}, R), \\ &R = \{R_1, R_2, ..., R_{K-1}, R_K\}, \\ &y_k = 0,1; k = 1, ..., K \end{aligned} \quad (1)$$

In this equation, R includes a set of missing indicator variables where $\Pr(R_k = 0)$ is the probability that Y_k is missing and K is the total number of variables. The algorithm is re-iterated until all pairwise correlations of the original and imputed data satisfy the criteria:

$$\left|\delta_{jk} - \delta_{jk}^{imp}\right| < c_{jk} \quad (2)$$

where δ_{jk}^{imp} and δ_{jk} are the pairwise correlations corresponding to the imputed and original data, respectively, for variables y_j and y_k, and c_{jk} is some constant defined individually for each correlation to minimize bias and increase coverage rate.

RESULTS

Our work is motivated by results showing a marginal association between recurrence and size obtained via ultrasound (p=0.06) despite no significant relationship between recurrence and mammographic size (p=0.74). Given that 70.20% of the ultrasound data was missing (Table 1), we pursued examining whether the significance of the relationship between tumor size and recurrence would change after multiple imputation employing the three previously described models. Examining assessment measures from the three models in Table 2 indicates adequate performance as average estimates of the pairwise correlations comparable to the original values, standardized biases less than 50%, small root mean squared errors (RMSE), coverage rates greater than 90%, and average widths of 95% confidence intervals for the pairwise correlations comparable to the widths of the original confidence intervals.

Figure 2 shows the distribution of tumor size obtained by ultrasound by recurrence group while Table 3 and Figure 3 present the distribution of p-values obtained from each of the ten imputations at each of the 1000 simulations. From Figure 2, we see that the difference in ultrasound data between recurrence groups is more pronounced when imputed under the model involving ultrasound tumor size and recurrence only and least pronounced in data imputed under the model including only ultrasound and mammogram

TABLE 2: Assessment measures of average estimates (AE), standardized biases (SB), root mean squared error (RMSE), coverage rates (CR) and average widths (AW) of 95% confidence intervals for pairwise correlations between ultrasound tumor size and recurrence and between ultrasound tumor size and mammogram tumor size imputed employing models with ultrasound tumor size and recurrence (Model 1), ultrasound tumor size and mammogram tumor size (Model 2), and ultrasound tumor size, mammogram tumor size, and recurrence (Model 3).

				SB		CR	
Model	Correlation	Original Estimate	AE	(All >50%)	RMSE	(All >90%)	AW
1	Ultrasound tumor size and recurrence	0.2234	0.2233	1.56%	0.0044	92.09%	0.2146
2	Ultrasound tumor size and Mammographic tumor size	0.5819	0.5820	2.94%	0.0032	91.74%	0.1499
3	Ultrasound tumor size and recurrence	0.2234	0.2215	18.79%	0.0078	92.74%	0.2176
3	Ultrasound tumor size and Mammographic tumor size	0.5819	0.5830	12.77%	0.0070	91.04%	0.1510
3	Mammographic tumor size and recurrence	0.0245	0.0256	19.02%	0.0053	94.65%	0.3932

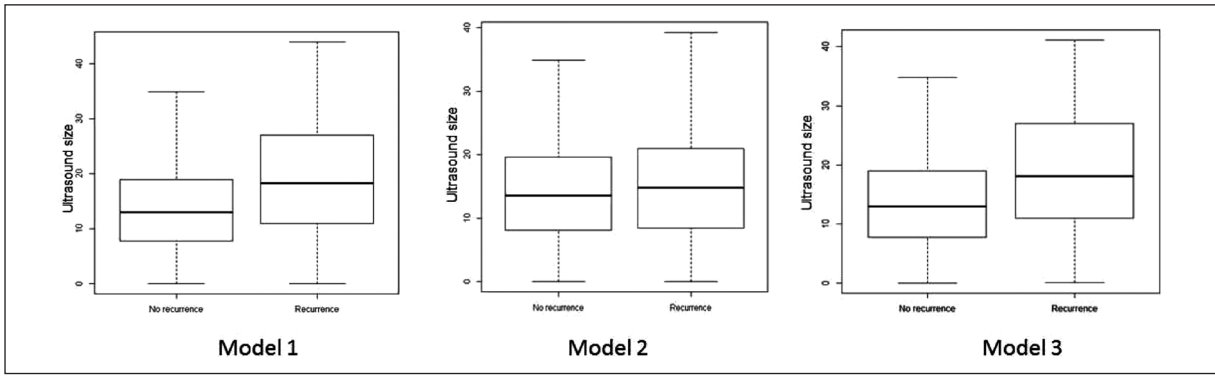

FIGURE 2: Distribution as presented by boxplots of ultrasound tumor size imputed employing models with ultrasound tumor size and recurrence (Model 1), ultrasound tumor size and mammogram tumor size (Model 2), and ultrasound tumor size, mammogram tumor size, and recurrence (Model 3).

measurements. A range of significant to insignificant values were associated with data imputed under the model including all three variables, as could be seen in the distribution of p-values in Table 3 and Figure 3.

These results indicate that the relationship of the imputed data with recurrence depends on which variables are included in the imputation model. While mammogram data appear to have an association with ultrasound data ($r = 0.58$, $p < 0.0001$), but they seem to decrease the association between ultrasound measurements and recurrence when included in the model. Thus, we infer that variable selection in the imputation model plays a

TABLE 3: Distribution of 1000 p-values obtained from the Wilcoxon rank-sum test comparing differences between recurrence groups in ultrasound tumor size imputed employing models with ultrasound tumor size and recurrence (Model 1), ultrasound tumor size and mammogram tumor size (Model 2), and ultrasound tumor size, mammogram tumor size, and recurrence (Model 3).

	Mean	Std Dev	Median	25th Pctl	75th Pctl	Minimum	Maximum
Model 1	0.000453	0.000634	0.000273	0.000136	0.000525	0.0000083	0.012
Model 2	0.3544	0.28	0.2822	0.1023	0.5543	0.000025	0.99
Model 3	0.000689	0.00532	0.000387	0.000100	0.000603	0.000011	0.17

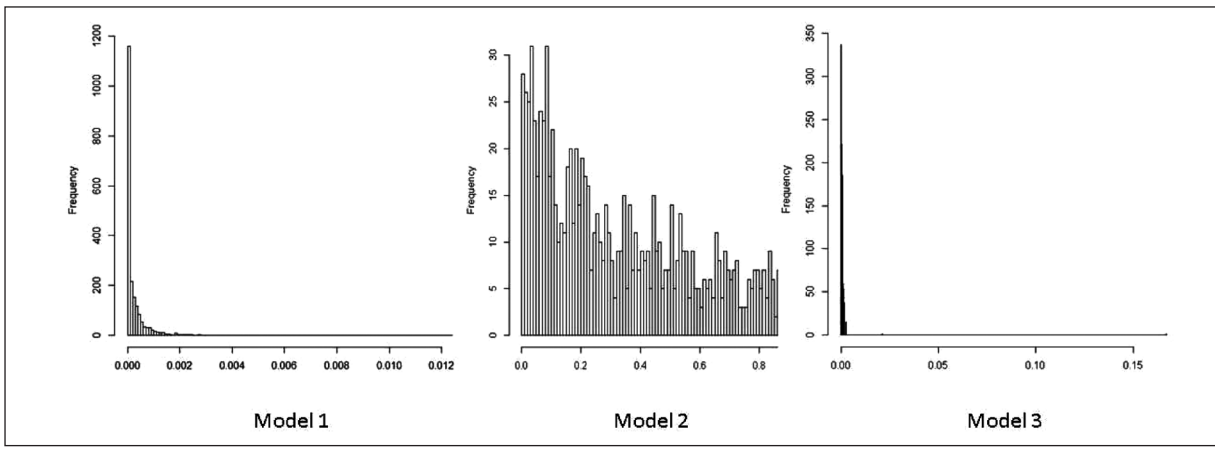

FIGURE 3: Distribution as presented by histograms of p-values obtained from the Wilcoxon rank-sum test comparing differences between recurrence group in ultrasound tumor size imputed employing models with ultrasound tumor size and recurrence (Model 1), ultrasound tumor size and mammogram tumor size (Model 2), and ultrasound tumor size, mammogram tumor size, and recurrence (Model 3).

key role when multiple imputation is applied to further investigate our association of interest.

CONCLUSION

In this work, we have shown how variable selection in imputation models could affect results obtained from imputed data. We pursued to explore the association between tumor size as measured by ultrasound and recurrence, observing a marginal relationship in complete case analyses. The significance of this association became more prominent in imputation models involving only the two variables but appeared less prominent in data imputed with models including tumor size measured by mammogram. The lack of an association between tumor size as measured by mammogram and recurrence observed in our complete case analyses may serve as an indication of its influence on the association between ultrasound data and recurrence. As the debate of which technology is superior in detecting breast cancer and predicting breast cancer recurrence has grown, multiple imputation may be one means of exploring comparisons in the performance of such detection procedures.

We focused on imputing ultrasound and mammogram data but could have included other prognostic factors. In our complete case scenario, univariate analyses indicated no difference in age ($p = 0.54$) between recurrence groups but significant difference in stage and grade with greater prevalence of recurrence among stages II/III and grades II/III (both p-values < 0.0001). Our imputation approach did not include models with these factors as the focus of this work was to examine the role of imputation on univariate analyses for evaluating the association between tumor size and recurrence. The implications of how imputation would affect the results of multivariate analyses will be the focus of future work. Nonetheless, these univariate analyses show our imputation approach as an application in exploring the performance of imaging technologies for predicting recurrence.

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