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Inverse Probability Weighted Least Squares Regression in the Analysis of Time-Censored Cost Data: An Evaluation of the Approach Using SEER-Medicare

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A B S T R A C T

Objectives: To assess the accuracy and precision of inverse probability weighted (IPW) least squares regression analysis for censored cost data. **Methods:** By using Surveillance, Epidemiology, and End Results-Medicare, we identified 1500 breast cancer patients who died and had complete cost information within the database. Patients were followed for up to 48 months (partitions) after diagnosis, and their actual total cost was calculated in each partition. We then simulated patterns of administrative and dropout censoring and also added censoring to patients receiving chemotherapy to simulate comparing a newer to older intervention. For each censoring simulation, we performed 1000 IPW regression analyses (bootstrap, sampling with replacement), calculated the average value of each coefficient in each partition, and summed the coefficients for each regression parameter to obtain the cumulative values from 1 to 48 months. **Results:** The cumulative, 48-month, average cost was $67,796 (95% confidence interval [CI] $58,454–$78,291) with no censoring, $66,313 (95% CI $54,975–$80,074) with administrative censoring, and $66,765 (95% CI $54,510–$81,843) with administrative plus dropout censoring. In multivariate analysis, chemotherapy was associated with increased cost of $25,325 (95% CI $17,549–$32,827) compared with $28,937 (95% CI $20,510–$37,088) with administrative censoring and $29,593 ($20,564–$39,399) with administrative plus dropout censoring. Adding censoring to the chemotherapy group resulted in less accurate IPW estimates. This was ameliorated, however, by applying IPW within treatment groups. **Conclusion:** IPW is a consistent estimator of population mean costs if the weight is correctly specified. If the censoring distribution depends on some covariates, a model that accommodates this dependency must be correctly specified in IPW to obtain accurate estimates.

Keywords: cost analysis, inverse probability weighting, observational data, accuracy and precision.

Introduction

Assessing the value of health care interventions often entails analyzing observational databases for cost information. Many databases available to health economists, such as insurance or practice databases, offer a fixed block of data for a specific calendar period, say January 2005 to December 2010. Researchers then identify specific patients within that block of data, according to the date of a particular diagnosis or treatment, and construct an analysis file in which patients with the event of interest are lined up by this "index date." Because the index dates invariably are distributed throughout the block of data, once patients are lined up their observation periods will differ simply by virtue of when, relative to the end of the block of data, they were identified. In our example, patients who do not die, or drop out of the database for other reasons before December 2010, will be censored at this time, and the later their index date the more likely they are to be censored. We refer to this as *administrative censoring*, because this type of censoring is an artifact of the way the data are provided and how researchers construct their analysis files. In private insurance or clinical practice databases, patients also may drop out during the period defined by the block of data, for instance, because they change health insurers or providers. An added complication is that patterns of censoring within observational data may vary by diagnosis or treatment modality. If one is interested in comparing the costs or outcomes of a newer versus established intervention, within a block of data defined by a fixed calendar period those receiving the newer intervention will have later index dates and, as a group, more administrative censoring.

Censoring poses particular problems for researchers interested in estimating the total treatment or lifetime costs for comparative cost or cost-effectiveness analyses, because the full costs rarely are observed for all patients in a study [1–8]. This problem was highlighted by Lin et al. [1], who proposed an estimator that they showed to be asymptotically unbiased when the censoring variable is discrete, and the partition boundary is chosen at those censoring times. Bang and Tsiatis [2] proposed another estimation method based on inverse probability weighting (IPW), and O'Hagan and Stevens [5] and Raikou and McGuire [6] showed that the two estimators are equivalent in some cases. Zhao et al. established the exact condition for the equivalency of the two estimators [9]. IPW has proved to be the more general approach and has been adopted and refined in subsequent publications by other researchers [10]. Recently, we used partitioned, IPW, least squares regression to estimate the long-term incremental costs associated

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with using granulocyte colony-stimulating factor to support initial adjuvant chemotherapy for early-stage breast cancer [11].

The objective of this study was to design and implement an experiment in which we first assembled a cohort of patients all of whom died within the block of data provided. We then simulated different patterns of censoring in this cohort that are consistent with the patterns typically encountered in economic analyses using insurance or practice databases, and we conducted a series of partitioned regression analyses in the cohorts with (using IPW) and without simulated censoring to examine the impact of different patterns of censoring on the cost coefficients from the IPW regression models.

Materials and Methods

Study Design and Setting

By using data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) cancer registry linked to Medicare [12–14], we identified a cohort of women who were diagnosed with metastatic breast cancer between January 1999 and December 2002, breast cancer was the first type of cancer diagnosed, they survived at least 60 days following diagnosis, they were continuously enrolled in Medicare Parts A and B from 12 months before diagnosis until death, and they died before the end of the Medicare claims data (December 2007). The rationale for selecting this cohort was that there was no administrative or dropout censoring and lifetime costs could be calculated for each patient. Medicare claims files linked to SEER consist of the following: Medicare Provider Analysis and Review, which includes all hospital (Part A) short stay, long stay, and skilled nursing facility bills; National Claims History, which includes all physician/supplier (Part B) bills; Outpatient, which includes all bills from institutional outpatient (Part B) providers; Home Health Agency, which includes all claims for home health services; Hospice; and Durable Medical Equipment. Medicare did not begin coverage for oral medications without an intravenous equivalent (Part D) until January 1, 2006, and Part D claims were not available for our study period. Nevertheless, our study included the vast majority of claims paid by Medicare for these patients.

Patients were required to have Medicare Part A and Part B coverage for at least 12 months prior to diagnosis to ensure that at least 12 months of claims were available to calculate an NCI Comorbidity Index score [15,16], to assess treatment history, and to eliminate the possibility of censoring because of switching from Part A/B coverage to health maintenance organization coverage. Patients were excluded if they met any of the following criteria: male sex, diagnosis made by death certificate or autopsy, or health maintenance organization coverage from 12 months before diagnosis until death.

Patient Characteristics

Patients were described according to their demographic, clinical, and socioeconomic characteristics, including age, race/ethnicity [17], histologic grade, and NCI Comorbidity Index [15,16,18,19]. Medicare claims were used to determine whether the patient received chemotherapy beginning within 60 days after the date of cancer diagnosis [20–22]. Chemotherapy beginning within this period was specified as a dichotomous variable. The same approach was used to classify patients according to whether they received radiation.

Direct Medical Costs

Medicare-paid amounts, obtained from claims files linked to SEER, were used to calculate the total direct medical cost to Medicare per patient per month (partition), from 60 days after the diagnosis of breast cancer for up to 4 years. All Medicare-paid amounts were inflated to 2009 US dollars by using the Hospital Input Price Index for Part A claims and the Medical Expenditure Index for Part B claims [23].

Introduction of Censoring

In the censoring simulations, patients were followed for up to 48 months ($T = y_1 = 48$) or the time of death (V_i), whichever came first. We assigned a random number x_i to each patient $i = 1, 2, \ldots, n$, which was uniformly distributed in the range [0,1]. In each of the censoring simulations, patients were assigned a censoring time C_i that was calculated by applying a suitable transformation to the random number x_i. Within the time horizon T, the simulated follow-up time (X_i) was then defined as $X_i = \text{Min}\{V_i, C_i\}$, the earlier of either the date of death or the simulated censoring time.

We simulated three types of censoring. First, we introduced *administrative censoring* and considered two alternative scenarios: One with a relatively short minimum observation period (y_0) within a fixed block of data ($y_0 = 6$ months) and a second with a longer minimum observation period ($y_0 = 24$ months). During y_0 there was no censoring, and censoring was assumed to be random and linear in time during the interval $y_1 - y_0$. The transformation for administrative censoring (C_i^A) was

$$C_i^A = y_0 + (y_1 - y_0) * (x_i^A) \quad (1)$$

A linear transformation in this instance is consistent with a situation commonly encountered in observational data, and specifically in SEER-Medicare. In SEER-Medicare, the diagnosis of cancer typically is evenly distributed during a specific time interval, and all patients who remain alive throughout the observation period are right censored at the same point in time (i.e., the end of the claims period). Consequently, once the patients are lined up by their date of diagnosis, administrative right censoring becomes evenly distributed in time.

Second, we introduced *dropout* (C_i^D) as an additional type of censoring, which was assumed to be random in time during the interval $y_1 - y_0$, with a rate λ, and so had an exponential (λ) distribution. The transformation for dropout censoring (C_i^D) was

$$C_i^D = y_0 + (y_1 - y_0) * \left(-\frac{\ln x_i^D}{\lambda}\right) \quad (2)$$

In this simulation, λ was set to natural logarithm of 2 (=0.7) such that when $x_i^D > 0.5$, and $y_1 - y_0 = 42$ months ($y_0 = 6$ months), greater than 50% of the censoring times exceeded T. We then selected the earlier of C_i^A and C_i^D as the censoring date ($C_i = \text{Min}\{C_i^A, C_i^D\}$). We did this for $y_0 = 6$ and 24 months.

Third, we introduced *differential administrative censoring in the chemotherapy group*, with $y_0 = 6$ months, to simulate the comparison of two different interventions of interest for cost with two different distributions of index dates within a block of data. In this simulation, purely for purposes of simulating differential censoring we supposed that chemotherapy for metastatic breast cancer is a newer treatment modality in metastatic breast cancer and that the index dates for beginning chemotherapy naturally would fall later in the block of data, thereby resulting in more administrative censoring in this group. We retained the same transformation for the nonchemotherapy group as in the administrative censoring-only simulations (Equation 1). In the chemotherapy group, we developed three new censoring distributions by using Equation 2 and $\lambda = 7.0$, $\lambda = 2.4$, and $\lambda = 1.2$.

Statistical Analysis

Prior to the introduction of censoring, we performed partitioned least squares regression analysis to examine adjusted associations between cumulative costs over 48 months and patient demographic,

clinical, and treatment factors. Separate regression analysis was performed for each of the 48 partitions. Coefficients for each patient factor were summed across the 48 partitions to obtain the cumulative, incremental cost associated with that factor. Confidence intervals (CIs) for the cumulative cost coefficients were calculated by using a bootstrap approach [24], in which the process of performing 48 partitioned regression analyses and summing coefficients across partitions was repeated 1000 times using sampling with replacement from the original cohort.

Censoring was then introduced, and we calculated the unadjusted average monthly and cumulative IPW cost for each of the censoring simulations. In IPW, each observed cost is weighted by the inverse of the probability of not being censored. The weights are estimated by a nonparametric estimator, which is a version of the Kaplan-Meier estimator in which the roles of death and censoring are reversed. This estimator takes the following form:

$$\hat{S}_c(t) = \prod_{t_j \le t} \frac{n(t_j) - c_j}{n(t_j)} \tag{3}$$

where the t_j values are the times at which censoring is observed to take place, $n(t)$ is the number of cases for which $X_i \ge t$ (i.e., the number of patients in the sample who are still alive and uncensored immediately before time t), and c_j is the number of cases that are censored at time t_j.

In this case, the observation period was divided into 48 monthly partitions. Within each partition, we applied IPW. Each patient uncensored at the end of a partition was given the corresponding IPW and that partition-specific IPW was multiplied by the partition-specific cost. Patients were assumed to have been censored at the end of the month, such that they contributed an observation to the month in which they were censored. The cohort average cost within each partition was summed across partitions to estimate the cumulative costs in the cohort accounting for censoring. This estimator takes the following form:

$$\hat{\mu}_2^T = \frac{1}{n} \sum_{i,k} \frac{d_i^k \tilde{M}_i^k}{\hat{S}_c(X_i^k)} \tag{4}$$

where $\hat{\mu}_2^T$ is the cumulative IPW cost at T, k denotes partitions 1,2, . . ., k, and $\tilde{M}_i^k$ is the partitioned cost. To identify whether a patient has been censored in partition k, $d_i = I\,(X_i = V_i)$, where $I(\cdot)$ denotes the indicator function, that is, $d_i^k = 1$ if and only if patient i is *not* censored in partition k.

One implication of Equation 3 is that within each partition, the sum of the weights $1 \big/ \hat{S}_c(t)$ is

$$\sum_{i=1}^{n} d_i \hat{S}_c(X_i)^{-1} = n \tag{5}$$

This was used to check the accuracy of the IPW computations.

We then repeated the partitioned least squares regression analyses for each of the censoring scenarios, as described above, by using the partition-specific IPWs to weight the observations in that partition. The cumulative and monthly regression coefficients for chemotherapy were plotted for the original cohort with no censoring, as well as for each of the simulated censoring scenarios.

To examine the frequency with which the 95% CIs for coefficients from the multivariate IPW analyses included the corresponding mean values from the analysis with no censoring, we conducted coverage probability analyses. We performed 30 iterations of the bootstrap process used to calculate the IPW coefficients and 95% CIs. In each iteration, the process of performing 48 partitioned regression analyses and summing coefficients across partitions was repeated 1000 times using sampling with replacement from the original cohort, as described above. For each of the iterations $i = 1,2, \ldots, 30$, we defined a binomial variable Z_i where $Z_i = 1$ if the 95% CI for the cost coefficient calculated from the 1000 bootstraps within the iteration included the corresponding cost coefficient from the analysis without censoring, and $Z_i = 0$ if it did not. The coverage probability was then calculated by summing the values of Z_i and dividing by 30.

Finally, we compared the findings from the IPW regression analysis with $C_i = \text{Min}\,\{C_i^A, C_i^D\}$ and $y_0 = 6$ months with two other approaches that, in the past, have been used to address the problem of censoring: one in which censored observations are dropped from the cohort prior to analysis and a second in which censored observations are included but treated as complete observations [7].

Table 1 – Patient characteristics.

Characteristic	n	%
	1500	100.0
Age (y)		
66–70	243	16.2
71–75	345	23.0
76–80	361	24.1
>80	551	36.7
Race/ethnicity		
White	1232	82.1
Black	164	10.9
Hispanic	NS*	NS*
Other	NS*	NS*
Year of diagnosis		
1999	215	14.3
2000	451	30.1
2001	437	29.1
2002	397	26.5
Tumor grade		
1	63	4.2
2	325	21.7
3	504	33.6
4	NS*	NS*
Missing	NS*	NS*
Estrogen (ER) and progesterone (PR) receptor status		
ER+ and PR+	507	33.8
ER+ or PR+	214	14.3
ER− and PR−	234	15.6
Unknown/missing	545	36.3
Chemotherapy began within 60 d of diagnosis		
No	1101	73.4
Yes	399	26.6
Radiation began within 60 d of diagnosis		
No	1234	82.3
Yes	266	17.7
NCI Comorbidity Index		
0	1025	68.3
1	283	18.9
2	NS*	NS*
≥3	NS*	NS*
Geographic area size		
Large metropolitan	926	61.7
Metropolitan	357	23.8
Urban	81	5.4
Less urban	NS*	NS*
Rural	NS*	NS*

* Data not shown because one or more cell has a count of fewer than 11.

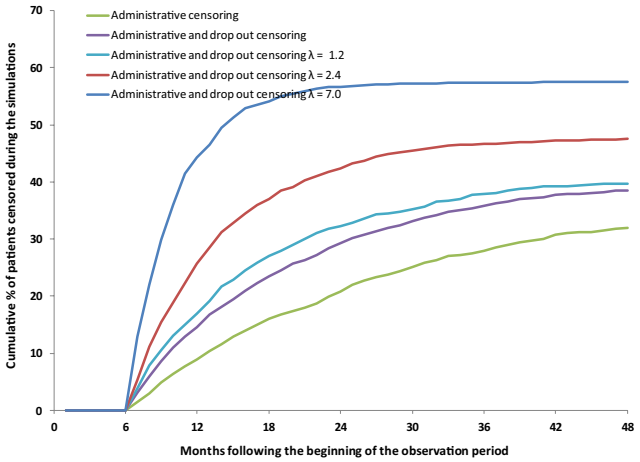

Fig. 1 – Censoring during the simulations (censoring begins after month 6). This figure presents the cumulative percent of patients censored (C_i) for the administrative censoring only (C_i^A) and administrative plus drop out (Min $\{C_i^A, (C_i^D)\}$) scenarios (4 scenarios with different rates of censoring), such that $C_i < V_i$, where V_i is the actual time of death. The lines are the mean cumulative percent of patients censored, calculated using a bootstrap approach, in which the process of obtaining C_i was repeated 1,000 times using sampling with replacement from the original cohort of 1,500 patients.

Results

There were 1500 patients in the cohort, 1339 (89%) of whom died within the 48-month observation period selected for the cost analyses (Table 1). Based on 1000 simulations using sampling with replacement from the cohort of 1500, the mean cumulative percent censored at 48 months was 32.0% for administrative censoring only and 38.5% for administrative plus dropout censoring at $\lambda = 0.7$, 39.6% at $\lambda = 1.2$, 47.6% at $\lambda = 2.4$, and 57.5% at $\lambda = 7.0$ (Fig. 1).

In the base-case population, the unadjusted average cumulative cost per patient was $67,796 (95% CI $58,454–$78,291) with no censoring, $66,313 (95% CI $54,975–$80,074) with administrative censoring ($y_0 = 6$ months), and $66,765 (95% CI $54,510–$81,843) with administrative plus dropout censoring ($y_0 = 6$ months). Average, unadjusted cumulative costs in the three scenarios were similar throughout the observation period (Fig. 2). Results were similar with $y_0 = 24$ months (not shown).

The adjusted incremental cumulative cost of chemotherapy was $25,325 (95% CI $17,459–$32,827) in the base-case analysis, $28,937 (95% CI $20,510–$37,088) after the introduction of administrative censoring ($y_0 = 6$ months), and $29,593 (95% CI $20,564–$39,399) after the introduction of administrative plus dropout censoring ($y_0 = 6$ months) (Table 2). More censoring was associated with less accurate IPW cost estimates for the chemotherapy coefficient (Fig. 3). All, however, except one of the coverage probabilities for the coefficients in the IPW regression analyses were 0.97 or higher (Table 2).

Adding censoring to the chemotherapy group resulted in estimated cumulative cost coefficients that were lower than in the base-case analysis (Fig. 4A, B). Weighting within the treatment groups (Fig. 4B), as compared with weighting across the groups (Fig. 4A), resulted in more accurate estimates and higher coverage probabilities at all rates of differential censoring (Fig. 5A, B).

Compared with using the IPW approach to address the problem of censoring, treating censored patients as deaths (Fig. 6) and excluding censored patients from the analysis (not shown) resulted in estimates that were both less accurate and less precise.

Conclusion

Observational data are increasingly popular for comparative effectiveness analysis and health economics research. Because health economics research often is concerned with estimating the full cost of care during an entire course of treatment, or until death, censoring in observational data poses a particular problem. The limitations of conventional approaches such as excluding those who are censored, or simply ignoring the fact that some patients are censored, are well-documented, and several approaches to estimating population means costs in the presence of censoring have been proposed in the past 15 years [1–10] and recently compared [7]. Direct comparison of the costs of alternative interventions in observational data requires adjustment for confounding, and previously we have used IPW, partitioned least squares regression to examine adjusted associations between supportive care in breast cancer and the long-term costs of care [11]. To evaluate the performance of IPW for estimating population costs under censoring, we designed an experiment in which we introduced simulated censoring into a cohort of patients all of whom died during the period defined by the data.

We found that partitioned IPW was accurate for estimating overall unadjusted costs under the types of administrative and dropout censoring researchers commonly encounter when using administrative and claims databases. For instance, the simulation in which we introduced both administrative and dropout censoring resulted in 39% of patients being censored by the end of the 48-month observation period. Yet, the estimated cumulative unadjusted cost by IPW was within 2% of the estimate with no censoring introduced. In this study, we observed that the greatest loss in the precision of the partitioned unadjusted cost estimates occurred between months 24 and 30, as the cumulative censoring approached one third of the entire cohort (500 patients). Our ob-

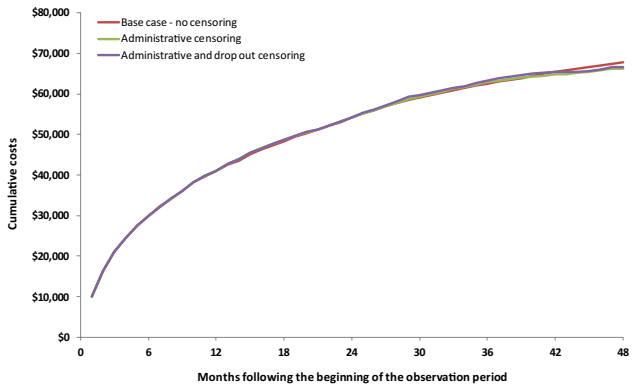

Fig. 2 – Unadjusted cumulative costs, with and without censoring (censoring begins after month 6). This figure presents the unadjusted, cumulative costs over 48 months in the 1,500 breast cancer patients who died during the study. The "Base case-no censoring" line depicts the actual mean cumulative costs among these patients over 48 months, without simulated censoring introduced. It is calculated by summing all costs in a month, dividing the sum by 1,500, and then adding that month's average to the sum of the previous months' averages. The cost curves for "Administrative censoring" and "Administrative and drop out censoring" are constructed by first applying the corresponding inverse probability weights (IPWs) to the costs of those who remain uncensored in that month, and then following the process described above. The means were calculated using a bootstrap approach, in which sampling with replacement of 1,500 from the original cohort was repeated 1,000 times.

Table 2 – Multivariate cost analysis (censoring begins at 6 mo).

Characteristic	No censoring			Administrative censoring				Administrative and dropout censoring			
	Regression coefficient	95% Confidence interval		Regression coefficient	95% Confidence interval		Coverage probability*	Regression coefficient	95% Confidence interval		Coverage probability*
Age (y)											
66–70	Reference category			Reference category				Reference category			
71–75	−2,412	−12,817	7,382	−3,122	−14,634	7,452	1.00	2,206	−10,555	13,881	1.00
76–80	−8,878	−18,535	465	−8,660	−18,870	2,256	1.00	−2,183	−13,975	8,917	1.00
>80	−19,221	−28,403	−10,290	−15,824	−24,663	−6,412	1.00	−12,187	−22,565	−1,688	1.00
Race											
White	Reference category			Reference category				Reference category			
Black	2,287	−7,416	13,006	2,832	−7,773	14,354	1.00	815	−10,455	13,475	0.90
Other	8,748	−14,132	39,724	3,636	−18,656	27,325	0.97	3,463	−20,310	30,535	1.00
Hispanic	10,619	−4,308	25,397	4,676	−11,327	20,895	1.00	4,321	−14,586	22,767	1.00
Year of diagnosis											
1999	Reference category			Reference category				Reference category			
2000	2,467	−5,900	11,049	−421	−10,631	8,801	1.00	3,914	−5,918	12,843	1.00
2001	3,552	−4,254	11,579	1,840	−8,490	11,833	1.00	5,736	−4,532	15,356	1.00
2002	13,794	5,062	22,910	10,119	205	19,453	1.00	11,655	510	20,945	1.00
Tumor grade											
1	Reference category			Reference category				Reference category			
2	15,735	3,900	27,111	19,908	6,313	33,488	1.00	18,832	5,034	32,918	1.00
3	15,052	3,331	27,142	20,629	9,555	32,722	0.97	22,205	9,539	34,915	1.00
4	9,372	−10,107	29,930	814	−15,281	16,312	1.00	−1,011	−17,897	15,575	1.00
Missing	2,749	−9,047	13,942	5,680	−5,983	17,046	0.97	4,073	−9,245	16,312	1.00
Estrogen (ER) and progesterone (PR) receptor status											
ER− and PR−	Reference category			Reference category				Reference category			
ER+ and PR+	17,499	6,840	27,394	18,268	9,200	27,996	1.00	18,691	7,747	29,090	1.00
ER+ or PR+	14,571	2,949	26,103	13,604	2,807	24,385	1.00	12,219	671	23,332	1.00
Unknown/missing	10,593	486	20,261	10,757	1,410	20,172	1.00	14,116	3,337	24,286	1.00
Chemotherapy began within 60 d of diagnosis											
No	Reference category			Reference category				Reference category			
Yes	25,325	17,549	32,827	28,937	20,510	37,088	1.00	29,593	20,564	39,399	1.00
Radiation began within 60 d of diagnosis											
No	Reference category			Reference category				Reference category			
Yes	1,755	−5,266	8,785	4,315	−3,204	11,824	1.00	3,687	−4,620	12,047	1.00
NCI Comorbidity Index											
0	Reference category			Reference category				Reference category			
1	−1,286	−7,866	5,673	−2,729	−9,990	5,006	1.00	−4,071	−11,095	4,270	1.00
2	4,460	−5,414	15,788	12,613	−88	25,565	1.00	8,206	−5,430	20,960	1.00
≥3	3,140	−8,173	14,789	3,742	−7,386	15,996	1.00	4,613	−7,587	17,591	1.00
Geographic area size											
Big metro	Reference category			Reference category				Reference category			
Metro	−13,303	−19,995	−6,895	−11,577	−18,608	−4,305	1.00	−13,536	−21,024	−6,453	1.00
Urban	−11,597	−23,095	366	−7,523	−21,510	6,022	1.00	−10,748	−26,273	5,407	0.97
Less urban	−21,086	−30,480	−10,193	−17,428	−28,908	−5,283	1.00	−20,674	−31,730	−8,991	0.97
Rural	−17,924	−33,340	−1,857	−4,391	−25,673	18,258	1.00	1,456	−26,834	30,335	0.97

* Coverage probability is the probability that the confidence interval contains the regression coefficient from the no censoring analysis, over 30 iterations of 1000 bootstrapped samples.

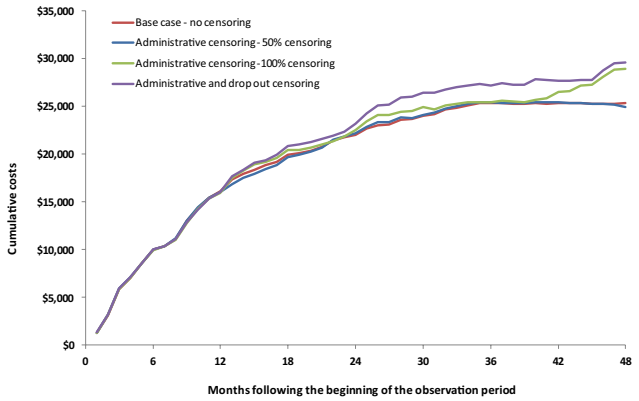

Fig. 3 – Cost coefficients for chemotherapy from the multivariate regression analyses (censoring begins after month 6). This figure presents the results from the partitioned, inverse probability weighted (IPW) least squares regression cost analyses performed using the cohort of 1,500 breast cancer patients who died during the observation period. The models included as covariates age, race/ethnicity, year of diagnosis, tumor grade, estrogen and progesterone status, whether chemotherapy was initiated within 60 days after diagnosis, whether radiation therapy was initiated within 60 days after diagnosis, National Cancer Institute Comorbidity Index and the geographic area size. The lines are the mean cumulative cost regression coefficients for chemotherapy (versus no chemotherapy, the reference category). These were calculated using a bootstrap approach in which the process of performing 48 partitioned regression analyses and summing coefficients across partitions was repeated 1,000 times using sampling with replacement from the original cohort. The "Base case-no censoring" line depicts the mean incremental cumulative cost of chemotherapy over 48 months without simulated censoring introduced. The "Administrative censoring" and "Administrative and drop-out censoring" lines represent the mean IPW incremental cumulative cost coefficients for chemotherapy over 48 months, with censoring beginning at 6 months. Administrative censoring also was reduced by 50% "Administrative censoring–50% censoring" to examine the impact on the accuracy of IPW.

servations regarding the performance of IPW in unadjusted analyses apply also to the multivariate analyses prior to the introduction of differential censoring, although we observed a greater loss in the accuracy of the chemotherapy cost coefficient, and it began earlier in the observation period around month 24.

Researchers using observational data to compare the costs of alternative treatments (especially newer vs older) may encounter the additional problem of differential censoring, in which once patients are lined up by their index date, those with newer treatments have more right censoring. In this study, IPW partitioned regression performed less favorably when we increased the amount of censoring in the chemotherapy group relative to the nonchemotherapy group. Adding censoring resulted in underestimating the incremental costs of chemotherapy under six separate scenarios that included changing the rate (λ) of censoring and whether IPW was applied to the cohort as a whole, or separately to the two treatment groups. Separate weighting for the individual treatment groups was considerably more accurate. We do suggest, therefore, that researchers intending to use IPW partitioned regression to compare the costs of alternative treatments should first examine patterns of censoring in their treatment groups, and if they are substantially different, should take steps to minimize these differences such as restricting the observation period or the enrolment period. Further, we recommend applying separate IPWs to treatment groups or other covariables of interest if they have different patterns of censoring.

As discussed above, several different approaches to the problem of censoring have been proposed in the literature. One limitation of our study is that we chose to evaluate only one of these approaches. Young [7] compared several different methods across four different censoring mechanisms according to their ability to

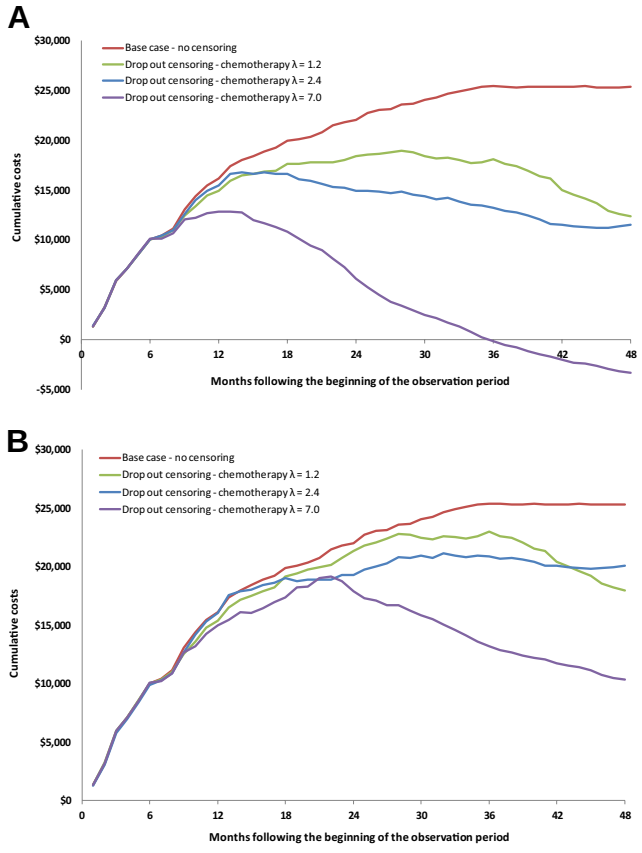

Fig. 4 – Cost coefficients for chemotherapy from the multivariate regression analyses—censoring added to the chemotherapy group (censoring begins after month 6). (A) Weighting across the entire cohort and (B) Weighting by treatment group. 4A presents the findings from the multivariate analyses, in which differential censoring was added to the chemotherapy group. The lines are the mean cumulative cost regression coefficients for chemotherapy (versus no chemotherapy, the reference category). The "Base case-no censoring line depicts the mean incremental cumulative cost of chemotherapy over 48 months without simulated censoring introduced. The "Drop out censoring–chemotherapy. . ." lines represent the mean IPW incremental cumulative cost coefficients for chemotherapy over 48 months, with increasing amounts of differential censoring (indicated by increasing values of λ) beginning at 6 months. Mean coefficients were calculated using a bootstrap approach, in which the process of performing 48 partitioned regression analyses and summing coefficients across partitions was repeated 1,000 times using sampling with replacement from the original cohort. 4B is identical to 4A, except that IPWs were calculated separately for the two treatment groups prior to performing the multivariate analyses.

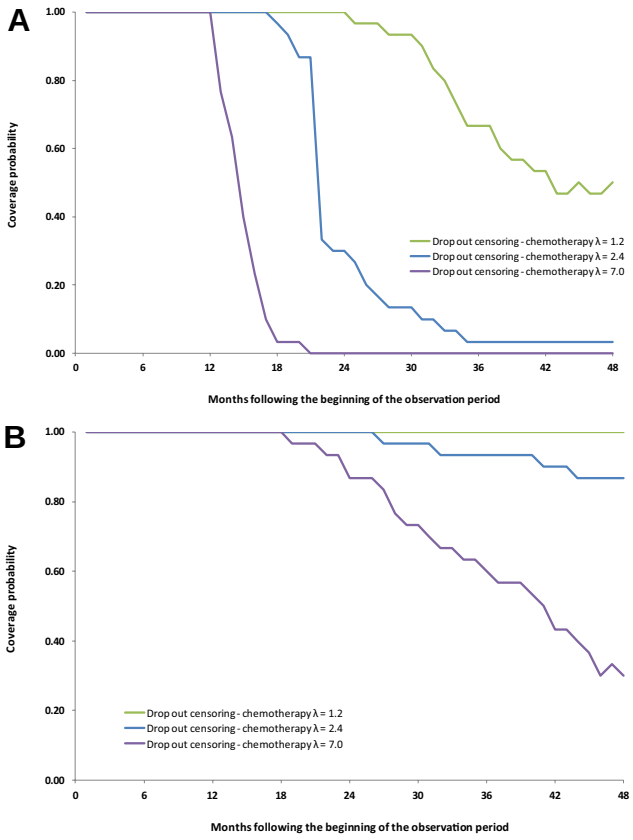

Fig. 5 – Coverage probabilities for regression coefficients in which censoring was added only to the chemotherapy group. (A) Weighting across the entire cohort and (B) Weighting by treatment group. In figure 5A, Coverage probabilities indicate the probability that the chemotherapy cost coefficient from the multivariate analysis with no censoring is within the 95% CI of the IPW coefficient from the censoring simulation. These were calculated by performing 30 iterations of the bootstrap process used to calculate the IPW coefficients and 95% CIs. For each of the iterations i = 1,2,. . .,30, we defined a binomial variable Z_i where Z_i = 1 if the 95% CI included the corresponding cost coefficient from the analysis without censoring, and Z_i = 0 if it did not. The coverage probability was calculated by summing the values of Z_i and dividing by 30. 5B is identical to 5A, except that IPWs were calculated separately for the two treatment groups prior to performing the multivariate analyses.

predict mean total costs and concluded that the weighted cost method with known cost histories —the approach we used—is the preferred method for obtaining an accurate estimate of the mean total cost alone and the uncertainty surrounding it. Also, IPW partitioned regression is relatively straightforward to implement, because there are simple checks to ensure that the weights are being calculated correctly. Moreover, the standard error of the mean is readily obtained by using a bootstrap approach.

A second limitation is that we did not include informative censoring among our simulations. Informative censoring occurs when patients withdraw from a study for reasons that are related to the event of interest, such as because of a drug-related adverse event in a clinical trial. Historically, one possible source of informative censoring in economic analysis of private insurance data was reaching the lifetime limit of insurance benefits. Another type of informative censoring occurs when a cost-generating event, such as hospitalization due to stroke, is followed by a transition to a site of service, for example, home health agency or long-term care facility where medical costs continue to accrue but for which data are not available.

We did not calculate coverage probabilities for unadjusted IPW costs, but the unadjusted cost curves overlapped for the entire 48 months, making it likely that coverage probabilities were extremely high. Also, it might be informative to have goodness-of-fit statistics for the simulations. The method we used, however, is nonparametric and cannot predict the distribution of costs within time partitions. Furthermore, our simulations were constructed such that all patients either died or were censored during the 48-month time horizon. An alternative approach would have been to allow a random subset who did not die during 48 months to remain alive until the end of this time period.

IPW estimators are biased when covariates affect survival [8]. We did not perform survival analysis in this study because the patients were selected on the basis of the fact that they died during the observation period, and we then truncated the observation period on the basis of the proportion of patients remaining alive at the end of that period. Consequently, it is likely that survival analysis would have produced biased estimates. Also, although we report coverage probabilities, as estimators become more inefficient with changing design points, coverage probabilities can improve even if the estimator is biased. Finally, our cohort was con-

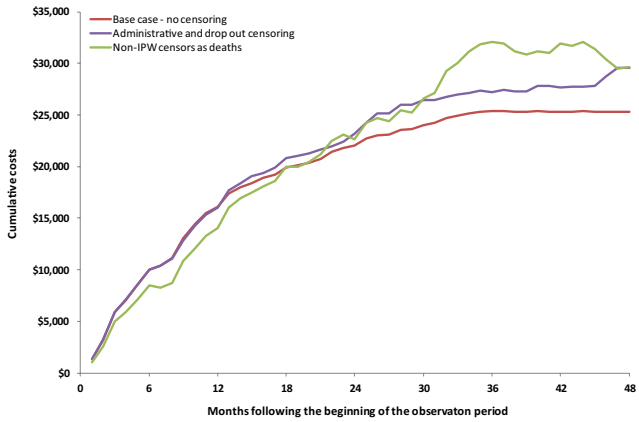

Fig. 6 – Regression analysis treating censored patients as deaths (censoring begins after month 6). IPW, inverse probability weighted. This figure presents the findings from the multivariate analyses, in which censored observations were treated as complete observations. The lines are the mean cumulative cost regression coefficients for chemotherapy (versus no chemotherapy, the reference category). The "Base case - no censoring" line depicts the incremental cumulative cost of chemotherapy over 48 months without simulated censoring introduced. The "Censoring addressed by inverse probability weighting" line represents the IPW incremental cumulative cost coefficient for chemotherapy over 48 months, with administrative and drop out censoring beginning at 6 months. The "Censoring addressed by treating censored patients as deaths" line represents an approach in which administrative and drop out censoring beginning at 6 months was introduced, but addressed simply by treating censored patients as complete observations. Mean cost coefficients were calculated using a bootstrap approach, in which the process of performing 48 partitioned regression analyses and summing coefficients across partitions was repeated 1,000 times using sampling with replacement from the original cohort.

structed from a selected group of patients for the purposes of an empirical test of the IPW regression method and is not intended to have relevance to the costs of care in breast cancer or the incremental cost of treatment.

Overall, IPW partitioned least squares regression performed well under a number of censoring scenarios commonly encountered in observational research. One particular source of concern, however, is differential censoring by treatment group, which is common in administrative and claims data. Researchers interested in using this approach to compare the costs of alternative treatments should first examine patterns of censoring in their treatment groups and take steps to minimize the limitations of IPW regression. Also, our findings should be confirmed by using other data sets that include patients with other patterns of enrolment in the database, clinical conditions, and patterns of cost accrual.

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