Does Higher Spending Improve Survival Outcomes for Myocardial Infarction? Examining the Cost-Outcomes Relationship Using Time-Varying Covariates

Deborah Cohen, Douglas G. Manuel, Peter Tugwell, Claudia Sanmartin, and Tim Ramsay

Objectives. Previous patient-level acute myocardial infarction (AMI) research has found higher hospital spending to be associated with improved survival; however, survivor-treatment selection bias traditionally has been overlooked. The purpose of this study was to examine the AMI cost-outcome relationship, taking into account this form of bias.

Data Sources. Hospital Discharge Abstract data tracked costs for AMI hospitalizations. Ontario Vital Statistics data tracked patient mortality.

Study Design. A standard Cox survival model was compared to an extended Cox model using hospital costs as a time-varying covariate to examine the impact of cost on 1-year survival in a cohort of 30,939 first-time AMI patients in Ontario, Canada, from 2007 to 2010.

Principal Findings. Higher patient-level AMI spending decreased the hazard of dying (Standard Model: log-cost hazard ratio: 0.513, 95 percent CI: 0.479–0.549; Extended Model: log-cost hazard ratio: 0.700, 95 percent CI: 0.645–0.758); however, the protective effect was overestimated by 62 percent when survivor-treatment bias was overlooked. In the extended model, a 10 percent increase in spending was associated with a 3.6 percent decrease in hazard of death.

Conclusion. The findings of this study suggest that if survivor-treatment bias is overlooked, future research may materially overstate the protective effect of patient-level spending on outcomes.

Key Words. Myocardial infarction, time-varying covariates, cost-outcome relationships, survivor-treatment selection bias

Decades of rising health expenditures in most industrialized countries have reinforced efforts to reduce costs while maximizing patient outcomes (OECD 2013). In the United States, the Affordable Care Act of 2010, designed to

broaden affordable health insurance coverage and curb growth in spending, has reinforced efforts to optimize value for money in health care (Fisher et al. 2009; Fisher and Skinner 2010). In Canada's universal health care context, in which health spending is publicly financed, the relationship between costs and outcomes and the corresponding return on investment is also a priority policy issue (Health Council of Canada 2009; Blomqvist and Busby 2012; Cohen et al. 2014a). A number of U.S. and Canadian studies have examined the relationship between health system spending and health outcomes, with most studies focusing on cost-outcome relationships at the hospital level (Fisher et al. 2003a, 2003b; Kaestner and Silber 2010; Silber et al. 2010; Romley, Jena, and Goldman 2011; Stukel et al. 2012). A rather limited number of studies have examined the cost-outcome relationship at the patient level, examining the association between actual patient costs and mortality (Schreyogg and Stargardt 2010; Stargardt, Schreyogg, and Kondofersky 2013).

Conducting cost-outcomes research at the patient level is challenging due to the observational nature of most study designs. Because it is often not practical or ethical to randomize patients to higher or lower cost treatment groups, researchers must address treatment selection bias—a form of bias in which systematic differences in patient baseline characteristics between different treatment groups can mask the true effect of the treatment on the outcome (Stukel et al. 2007). A second form of bias called “survivor-treatment selection bias,” however, is often overlooked in outcomes research (Glesby and Hoover 1996; van Walraven et al. 2004). Survivor-treatment selection bias, also known as “time-dependent bias” occurs when the timing of the treatment in relation to survival is not accounted for. Patients who live longer and who may be healthier than patients who die early are also more likely to receive treatment. In this context, an ineffective treatment can appear erroneously to improve survival simply because healthier patients live long enough to receive treatment (Glesby and Hoover 1996; Fisher and Lin 1999). We argue that this form of bias extends beyond treatment-outcome studies to research focused

Address correspondence to Deborah Cohen, Ph.D., Department of Population Health, University of Ottawa, Institute for Clinical Evaluative Sciences, 35 Soho Crescent, Ottawa, ON, Canada K1N6N5; e-mail: deborah.cohen@rogers.com. Douglas G. Manuel, M.D., F.R.C.P.C., M.Sc., is with the Ottawa Hospital Research Institute, University of Ottawa, Institute for Clinical Evaluative Sciences, Ottawa, ON, Canada. Peter Tugwell, M.D., F.R.C.P.C., M.Sc., is with the Centre for Global Health, Institute of Population Health, Ottawa Health Research Institute, University of Ottawa, Ottawa, ON, Canada. Claudia Sanmartin, Ph.D., is with the Health Analysis Division, Statistics Canada, Ottawa, ON, Canada. Tim Ramsay, Ph.D., is with the Ottawa Hospital Research Institute, Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, ON, Canada.

on the relationship between costs and outcomes, because the longer a patient is available to receive treatment, the greater the corresponding likelihood for increased costs. Without adjusting for the time-dependent nature of cost, patient-level research may overstate the importance of higher spending in relation to survival.

The relationship between cost and outcomes for acute myocardial infarction (AMI) provides a useful case study to assess the potential impact of survivor-treatment selection bias. AMI is an acute condition requiring immediate hospitalization and has a well-established care trajectory in which patient costs accumulate over time (Hassan et al. 2010). Previous research that has examined AMI hospital costs and mortality outcomes at the patient level using econometric methods has generally reported a relationship between higher spending and improved patient survival; however, this relationship may be overstated because these studies did not account for survivor-treatment selection bias (Newhouse and McClellan 1998; Schreyogg and Stargardt 2010; Stargardt et al. 2013). To assess the potential impact of survivor-treatment selection bias on AMI costs and outcomes, we compared a traditional Cox proportional hazard survival model to an extended Cox survival model in which hospital costs were treated as time-varying covariates (Therneau and Grambsch 2000). This study posed the following two research questions. First, does increased acute care spending at the patient level improve AMI survival outcomes in Canadian hospitals when survivor-treatment bias is accounted for? And second, to what extent does the time-varying nature of spending affect the size of the apparent relationship between AMI costs and outcomes? We believe that this study represents the first application of the time-varying extended Cox methodology to address the temporal nature of cost in relation to AMI survival.

METHODS

All patients between the ages of 40 and 105 years of age, admitted to Ontario hospitals with a most responsible diagnosis of AMI (ICD-10 code [I21]) between April 1, 2007, and March 31, 2009, were included in the cohort. Incident AMI cases were established by examining previous hospital discharge records for up to 15 years prior to the index AMI event. Patients were required to be residents of Ontario, Canada, for the duration of the study period to ensure that all services could be accurately tracked. Patients living in the Kingston/Quinte/Rideau region were excluded due to alternative billing

arrangements in which services could not be captured with available data sources.

Unique coded identifiers were used to link patient hospital records with the Ontario's Registered Persons Database to establish date of death for up to 1 year following the index AMI admission. The complete follow-up period for the study ranged between April 1, 2007, and March 31, 2010.

Data Sources

Total hospital spending for the index AMI episode of care and 1-year AMI hospital readmissions were studied in a cohort of 30,939 first-time AMI patients in Ontario, Canada. Hospital costs represented all inpatient services, including nursing and allied health staffing, diagnostics and procedures, and pharmaceuticals. Resource intensity weights (RIWs) in the Canadian Institute for Health Information (CIHI) Discharge Abstract Database were used to determine the intensity of hospital resource use based on standard Canadian case mix classification groups (CIHI 2004). The RIW was multiplied against the 2008 average cost per weighted case for Ontario hospitals to establish a total in-hospital cost for each episode of care (CIHI 2013). Physician billing costs from Ontario's Hospital Insurance Plan database, which are not included as part of the RIW, were added to the hospital cost based on corresponding admission and discharge dates for the AMI hospitalization and subsequent readmissions within 1 year for any ICD-10 code I (cardiac-related disease classification). Details of the costing methodology have been documented elsewhere (Cohen et al. 2014b). Patient's urban/rural status and socioeconomic status based on neighborhood income were determined using an area-based methodology in which the full patient postal code was linked with the 2006 Census neighborhood data from Statistics Canada.

Survival Models

A standard Cox survival model was compared to an extended Cox survival model to examine the time-varying nature of AMI inpatient costs on patient mortality over 1 year. In both models, the outcome variable was all-cause mortality. Costing data were log transformed using the natural log to adjust for heavy right skewness in the distribution (Diehr et al. 1999). In the standard Cox model, the time-varying nature of cost was not accounted for, and total costs were assigned to each patient at baseline. In the extended Cox survival

model, the time-varying nature of cost was modeled by allowing a patient's costs to change with time as costs were accrued for each hospitalization. Other covariates in the model included patient characteristics (including age at the time of AMI, sex, patient's urban/rural status, and socioeconomic status), patient comorbidities (including diabetes with complications, cerebrovascular disease, coronary heart failure, acute renal failure, chronic renal failure, pulmonary edema, malignancies, shock, and cardiac dysrhythmia as per the Ontario Mortality Prediction Rules [Tu et al. 2001]), infarct information (including ST segment elevation [STEMI], non-STEMI, and unknown), hospital characteristics (including AMI patient volumes and teaching hospital status), and year of index AMI.

All covariates were included in both models for the purposes of comparison. Robust variance estimation was used in both the standard and extended Cox models to correct for dependence among patients treated within the same hospital (Therneau and Grambsch 2000; Allison 2010). Collinearity among predictor variables was determined to be acceptable based on a variance inflation factor cutoff of 10 (Stevens 1996). The Wald Chi-square test was used to examine the overall fit of each model as well as the significance of beta coefficients for each covariate in the model. Hazard ratios (HRs) were used to express the instantaneous risk of events associated with each covariate in the model, when other covariates were controlled for. The percentage change in the hazard ratios of the costing variable was used to determine the size of the survivor-treatment selection bias between the standard and extended Cox models. Given the log transformation of the cost variable in the survival models, the log-transformed cost coefficient was used as a direct estimate of the partial elasticity of the hazard of dying with respect to spending (Culyer and Newhouse 2000). Partial elasticity was used for the interpretation of the relationship between spending and outcomes to determine a proportional effect of patient-level costs on the likelihood of dying.

Technical Details of the Extended Cox Model

In the extended Cox model, cost accumulated over time, increasing as a step function with each new rehospitalization. Because of the nature of the illness and hospitalization process, cost did not increase at regular intervals, but it was dependent upon each patient's hospital event and corresponding length of stay. As such, the cost data were modeled as an accumulating step function to reflect as closely as possible the true behavior of the cost function in health care (Lin 2003). For example, each patient was assigned a baseline log cost of

0 at the beginning of the index AMI admission. A new patient cost was then assigned on the date of discharge, based on the RIW and cost per weighted case associated with that episode of care. If a patient was readmitted to hospital a second time, a new patient cost was assigned on the date of discharge for the second hospitalization. If a third hospitalization occurred, a new patient cost was assigned on the date of discharge for the third hospitalization. Patient costs were accrued across time for every hospital discharge until all hospitalizations were accounted for. Records were coded using the counting process in *SAS* 9.2 for PROC PHREG, such that only one start and stop record for each patient was part of any instantaneous risk set within the extended Cox survival model (Allison 2010). See Appendix SA2 for an example of the patient data using the counting process.

In the extended Cox model, cost and survival were allowed to co-vary with time on either side of the regression equation. Instantaneous risk of death was calculated within risk sets for each event time, based on a patient's time-specific cost. The basic patient-level statistical model was as follows:

$$\log h_i(t) = \alpha(t) + \beta_1 \cdot X_1(t) + \beta_{2-18} \cdot X_{2-18},$$

where $\log h(t)$ was the instantaneous hazard for mortality at time t following the AMI event, given the baseline hazard $\alpha(t)$ when all covariates were zero, the time-varying covariate log cost ($X_1(t)$), and all other static variables (X_{2-18}). In the extended Cox model, only the cost variable was treated as a time-varying covariate. All other variables in the model were treated as time invariant and fixed at baseline.

We examined nonproportionality among all variables in the model. We also used a baseline model to examine the cost-outcome relationship in specific patient examples (e.g., a female patient at age 55 and 75 with multiple comorbid illnesses, a male patient age 65 with no comorbid illness). In each of these additional baseline analyses, there were no substantial changes to the relationship between AMI costs and patient mortality outcomes. The study was approved by the Ottawa Hospital Research Ethics Board, Ottawa, Ontario, Canada.

RESULTS

Table 1 presents the patient and hospital characteristics for the cohort studied, and 1-year follow-up costs. A total of 30,939 patients were included in the study cohort, with an average age of 69 at the time of the index AMI event.

Table 1: Characteristics of the Study Cohort

<i>Patient Characteristics</i>	<i>%</i>	<i>N</i>
Total AMI patient sample		30,939
Mean age (SD)	68.6 (13.9)	
Sex—% female	37.32	11,546
Patient residence—% rural	14.36	4,444
SES*—Low	43.75	13,535
SES—Medium	38.30	11,851
SES—High	17.95	5,553
Patient comorbidities [†]		
Diabetes with complications	0.91	282
Cerebrovascular disease	2.58	798
Coronary heart failure	18.28	5,657
Acute renal failure	5.73	1,774
Chronic renal failure	6.81	2,106
Pulmonary edema	2.12	656
Malignancies	3.09	956
Shock	2.95	912
Cardiac dysrhythmia	14.55	4,503
Infarct information		
Stemi	29.50	9,128
Nonstemi	54.86	16,973
Unknown	15.64	4,838
<i>Hospital Characteristics</i>	<i>%</i>	<i>N</i>
Total number of hospitals		162
Mean number of AMI cases (SD)	327 (389)	
Teaching hospital	7.44	12
Year of index AMI hospitalization		
2007	36.68	11,349
2008	51.20	15,846
2009	12.12	3,750
<i>One-year follow-up costs</i>	<i>Mean</i>	<i>SD/IR</i>
Mean actual costs	20,741	SD 24,012
Median actual costs	13,363	IR 15,043
Median log cost	9.500	IR 1.004
25th percentile cost	8,699	
75th percentile cost	23,742	

*Area-based income methodology used based on income distribution in the 2006 Ontario Census data from Statistics Canada.

[†]Comorbid illnesses based on Ontario Acute Mortality Prediction Rules (Tu et al. 2001).

AMI, acute myocardial infarction; IR, interquartile range; SD, standard deviation; STEMI, STsegment elevation myocardial infarction.

Table 2: Mortality and Hospital Admission Rates

<i>Patient Mortality Rates</i>	<i>%</i>	<i>N</i>
7 days	6.83	2,112
30 days	10.64	3,292
90 days	13.60	4,208
365 days	19.15	5,924
Patient hospitalization information	Mean/Median	SD/IR
LOS in days for first episode of care (mean/SD)	6.50	SD (10.05)
LOS in days for first episode of care (median/IR)	4.0	IR (2–7)
Total hospital days within 1 year (mean/SD)	10.78	SD (15.24)
Total hospital days within 1 year (median/IR)	6.0	IR (4–12)
Number of discharges range	1–11	
Patient readmission information	%	<i>N</i>
0 Readmissions	65.80	20,358
1 Readmission	19.72	6,101
2 Readmissions	7.96	2,463
3 or more readmissions	6.52	2,017

Note: Episode of Care represents the complete set of consecutive hospitalizations for the first acute myocardial infarction hospitalization.

LOS, length of stay.

Rates of comorbid illness and infarct status for AMI patients were consistent with previous estimates. The median patient cost for a 1-year follow-up period was \$13,363 in 2008 constant dollars (IR: 8,699–23,742). Table 2 presents patient mortality rates, patient hospitalization information, and number of readmissions within the AMI cohort. Within 1 year, 19 percent of the patients in the cohort died, and 34 percent of the patients had been readmitted at least once.

Table 3 presents results of both standard and extended Cox regression models. In both models, age was a significant predictor of survival outcomes (increasing hazard of death by 6 percent for every year aged) (extended Cox HR: 1.064, 95 percent confidence interval [CI]: 1.061–1.067), as were all comorbid illnesses with the exception of pulmonary edema. In both models, the presence of shock was the strongest predictor of death with more than a six-time increase in risk of death (extended Cox HR: 6.147, 95 percent CI: 5.423–6.968), followed by malignancies with a two-and-a-half-time increase in risk of death (extended Cox HR: 2.498, 95 percent CI: 2.241–2.784), and acute renal failure with just less than a two-time increase in risk of death (extended Cox HR: 1.966, 95 percent CI: 1.775–2.178).

In comparing the hazard ratios between the two models, the size of the cost-outcome effect was overestimated when the time-varying nature of cost

Table 3: Results of Standard and Extended Cox Survival Model—Examining the Relationship between Log Costs and Survival Outcomes

	Standard Cox Model (Time-Invariant)				Extended Cox Model (Time-Varying)					
	Hazard Ratio	95% CI	Coefficient	SE	p-value	Hazard Ratio	95% CI	Coefficient	SE	p-value
Log costs	0.513	0.479–0.549	−0.667	0.03	<.0001	0.700	0.645–0.758	−0.357	.04	<.0001
Age	1.061	1.058–1.064	0.059	.001	<.0001	1.064	1.061–1.067	0.062	.001	<.0001
Sex (M vs. F)	1.077	1.007–1.152	0.074	0.03	0.029	1.053	0.984–1.127	0.053	0.03	0.135
Rural patient	1.061	0.972–1.158	0.059	0.04	0.187	1.080	0.993–1.175	0.077	0.04	0.074
SES (low vs. high)	1.103	1.013–1.203	0.097	0.04	0.024	1.077	0.989–1.173	0.075	0.04	0.087
SES (mid vs. high)	1.077	0.992–1.168	0.074	0.04	0.076	1.060	0.978–1.148	0.058	0.04	0.156
Diabetes with complication	1.606	1.303–1.978	0.473	0.11	<.0001	1.455	1.189–1.781	0.375	0.103	0.0003
Cerebrovascular disease	1.930	1.693–2.199	0.657	0.07	<.0001	1.800	1.577–2.054	0.587	0.07	<.0001
Coronary heart failure	2.092	1.961–2.232	0.738	0.03	<.0001	1.812	1.696–1.935	0.594	0.03	<.0001
Acute renal failure	2.145	1.936–2.376	0.763	0.05	<.0001	1.966	1.775–2.178	0.676	0.05	<.0001
Chronic renal failure	1.259	1.127–1.406	0.230	0.06	<.0001	1.189	1.067–1.325	0.173	0.05	0.0017
Pulmonary edema	1.116	0.951–1.310	0.109	0.08	0.178	1.032	0.881–1.210	0.031	0.08	0.693
Malignancies	2.535	2.279–2.819	0.930	0.05	<.0001	2.498	2.241–2.784	0.915	0.06	<.0001
Shock	6.521	5.757–7.387	1.875	0.06	<.0001	6.147	5.423–6.968	1.816	0.06	<.0001
Cardiac dysrhythmia	1.163	1.081–1.252	0.151	0.04	<.0001	1.087	1.010–1.171	0.084	0.04	0.027
STEMI (vs. NonSTEMI)	1.070	0.986–1.161	0.067	0.04	0.106	1.071	0.982–1.169	0.068	0.04	0.119
Unspecified (vs. NonSTEMI)	1.679	1.541–1.830	0.518	0.04	<.0001	1.744	1.604–1.898	0.556	0.04	<.0001
Year 2008 (vs. 2007)	1.036	0.979–1.097	0.035	0.03	0.219	1.040	0.982–1.102	0.039	0.03	0.177
Year 2009 (vs. 2007)	1.020	0.930–1.120	0.020	0.05	0.671	1.016	0.927–1.114	0.016	0.05	0.729
Hospital AMI cases (per 50 cases)	0.996	0.993–0.999	−.00007	0.000	0.155	0.993	0.989–0.996	−.0002	0.000	0.004
Teaching hospital	1.019	0.895–1.159	0.019	0.07	0.778	0.962	0.851–1.087	−.039	0.06	0.534

Note: A comparison of hazard ratios for log costs in the two difference models were calculated as follows. For the standard Cox model, a hazard ratio of 0.513 corresponded to a 48.7% decrease in the risk of dying. For the extended Cox model, a hazard ratio of 0.700 corresponded to a 30.0% decrease in the risk of dying. A standard percentage change algorithm was then applied (standard Cox HR—extended Cox HR/extended Cox HR). ((48.7–30.0)/30.0 = 62.3%). This represented a 62% overestimation of the protective effect of cost on survival when survivor-treatment bias was not accounted for.

was not adjusted for. In the in the standard Cox model, a one unit increase in log cost was associated with a 49 percent decrease in the hazard of dying (HR: 0.513, 95 percent CI: 0.479–0.549). However, in the extended Cox model, which adjusted for survivor-treatment bias, the same expenditure was associated with a 30 percent decrease in the hazard of dying (HR: 0.700, 95 percent CI: 0.645–0.758). This represents a 62 percent overestimation of the benefit of higher spending, almost two-thirds of the total effect, when survivor-treatment bias was not taken into account.

Using the log-transformed cost coefficient, partial elasticity was used to interpret the proportional relationship between patient-level cost and the hazard of dying. In the extended Cox model in which survivor-treatment selection bias was accounted for, a 10 percent increase in spending was associated with a 3.6 percent decrease in the hazard of dying.

DISCUSSION

The goal of this study was to examine the relationship between inpatient costs and AMI outcomes while addressing survivor-treatment bias by modeling cost as a time-varying covariate. We observed a significant relationship between increased inpatient spending and decreased mortality in a cohort of AMI patients in Ontario, Canada, between the years of 2007 and 2010. In the extended Cox survival model, in which survivor-treatment selection bias was accounted for, a 10 percent increase in spending at the patient level was associated with a 3.6 percent decrease in the hazard of dying. However, the size of the protective effect of spending was overestimated by 62 percent, approximately two-thirds of the total treatment effect, when the time-varying nature of inpatient cost was not accounted for. This finding suggests that if survivor-treatment bias is overlooked, future research examining the relationship between AMI costs and outcomes may materially overstate the protective effect of patient-level spending on outcomes.

Survivor-treatment bias is often overlooked in health outcomes studies, and it may point to an important methodological gap in the literature. A systematic review in 2006 found that more than 60 percent of outcome studies in leading health care journals were susceptible to survivor-treatment selection bias, and that this bias had the potential to alter respective study conclusions in more than half of the studies affected (van Walraven et al. 2004). We believe that the present study represents the first to address the potential for survivor-treatment bias for AMI costs on survival outcomes.

The present study results are consistent with research that has demonstrated an overestimation of the treatment effect when survivor-treatment selection bias is overlooked (van Walraven et al. 2004; Austin et al. 2006; Sy et al. 2009; Levesque, Hanley, and Suissa 2010; Liu et al. 2012). Beyersmann et al. (2008) developed a mathematical proof that demonstrated the overestimation effect of survivor-treatment bias—noting that “in the case of a time-dependent exposure that prolongs time until the study endpoint, the prolonging effect will be overestimated” if survivor-treatment bias is overlooked. Austin et al. (2006) conducted Monte Carlo simulations to quantify the impact of survivor-treatment bias. They demonstrated that the survivor-treatment effect creates a negative or downward bias resulting in a treatment effect that appears to be more protective than it truly is. It should be noted that the current mathematical proofs and simulation studies available have evaluated the impact of survivor-treatment bias in which the time-varying treatment variable was binary (e.g., the presence or absence of surgery, transplant, drugs, etc.) (Austin et al. 2006; Beyersmann et al. 2008). In the present study, the time-varying explanatory variable—cost—was continuous. It is possible that for explanatory variables that are continuous, the direction of the bias is not always downward or negative. The results of our study, however, are consistent with previous work finding a downward direction of the bias.

In our study when the time-varying nature of cost was overlooked, the size of the protective effect was overestimated by 62 percent. We propose that like treatment effects, cost effects must be considered within the context of immortal time. Immortal time was first described as the period of time prior to the start of treatment in which the treatment could not meaningfully influence survival (Gail 1972). In a time-fixed traditional Cox survival model, an overestimation of the treatment effect occurs because this “untreated” immortal person time is incorrectly misclassified as “treated” person time, which inappropriately extends the time between the treatment and the outcome. The misclassification of person time results in biasing in favor of the treatment. In the case of cost data, when total costs are inappropriately assigned to the start of the study, this incorrectly extends the time between spending and the outcome, resulting in the misclassification of person time that biases in favor of higher spending.

It is important to note that we do not propose the time-varying methodology as being a replacement for, or superior to, traditional methods used to address general treatment selection bias in observational cost-outcomes health research. Instead, it is proposed as a complementary method to account for survivor-treatment selection bias. The instrumental variables

methodology holds considerable promise in cost-outcomes research (Stukel et al. 2007; Rassen et al. 2009) in that it goes beyond traditional epidemiological methods to address unobservable heterogeneity in the data. This technique, often employed in the field of health economics, is particularly relevant for health care outcomes research given that the majority of data sources are administrative in nature and patient records often lack sufficient clinical detail and refined patient characteristic information to fully adjust for all underlying differences between treatment groups (Ayanian 1999). However, standard instrumental variable techniques fail to deal well with time-varying covariates and corresponding survivor-treatment selection bias (Hernan and Robins 2006). Alternatively, marginal structural models can be used to estimate the effect of time-dependent covariates on time-to-event outcomes, when there is a risk of time-dependent confounding with other covariates in the model. Marginal structural models have typically been used in the field of epidemiology for patient-level treatment-outcome studies when there is concern for a time-dependent confounder that is also affected by previous treatment along a causal pathway (Hernan, Brumback, and Robins 2000; Robins, Hernan, and Brumback 2000; Bodnar et al. 2004). The present study did not examine the issue of time-dependent confounding. To our knowledge marginal structural models have not been used in the examination of the relationship between costs and outcomes at the patient level. The development of new research methods that combine the advantages of time-varying covariates, marginal structural models, and instrumental variables analysis will likely yield the most robust estimates to study the relationship between costs and outcomes. This study encourages support for the further examination of each of these methods in studying cost-outcome relationships at the patient level.

This study has several limitations that warrant consideration. First, the RIWs (CIHI 2004) used to calculate per patient hospital costs represent a relative value measuring total patient resource use in relation to an average typical acute care inpatient. As such, patient costs in this study represented an averaged value, depending upon the services received and case mix classification assigned, rather than a precise individualized cost estimate. This may have reduced costing variability among patients in the cohort. To address this issue, patient-specific physician billing fees were added to each patient's total cost based on hospital admission and discharge dates to enrich the costing data with a greater level of granularity.

Second, to measure the impact of survivor-treatment bias within the cost variable, we examined only the time-varying effect of cost. This approach was

selected for the sake of simplicity of interpretation, to isolate and measure the size of the survivor-treatment bias for cost. However, as a result, the findings do not reflect the time-varying nature of other covariates in the model, which were held fixed at baseline in both the time-fixed and time-varying models.

Third, findings from this study, in which a 10 percent increase in spending for AMI inpatients produced a 3.6 percent reduction in the hazard of dying, must be interpreted with caution. Because of study design, it was not possible to determine which components of patient-level care led to better survival outcomes. A sizeable research literature has explored AMI treatment-outcome relationships with respect to cardiac diagnostic technologies, percutaneous coronary intervention, and coronary artery bypass grafting (van der Werf et al. 2003; Alter, Stukel, and Newman 2006; Hassan et al. 2010; Maurice et al. 2014); however, future research that explores the linkage between inpatient spending, the use of specific AMI care, and patient mortality outcomes is warranted. It would not be appropriate to simply conclude from the present analysis that spending more will produce better outcomes without a more extensive examination of how dollars are spent to most effectively optimize outcomes (Fisher and Skinner 2010; Stukel et al. 2012).

Finally, results from this Canadian study may not be generalizable to the U.S. health care model. Previous hospital-level research in Canada has demonstrated that higher spending intensity in hospitals was associated with lower 30-day mortality rates (Stukel et al. 2012); however, this relationship has not been consistently demonstrated in the United States. While some hospital-level studies have demonstrated a relationship between higher spending and lower patient mortality (Kaestner and Silber 2010; Silber et al. 2010; Romley, Jena, and Goldman 2011), other studies have found little to no relationship between hospital spending and patient outcomes (Fisher et al. 2003a,b; Yasaitis et al. 2009). These findings may be attributed to differences in overall health system efficiency between the two countries and in the relative supply of medical human and technological resources (Fisher et al. 2009; Stukel et al. 2012). Future work that compares patient-level cost-outcome relationships for U.S. AMI patients is warranted to examine the generalizability of the findings to the American context.

CONCLUSION

By examining the relationship between patient-level AMI spending and survival in Ontario, Canada, this study addressed a key methodological issue that

has important health policy implications. We found a significant relationship between increased patient-level spending and decreased 1-year mortality. However, our work also demonstrated a substantial overestimation of the size of the protective effect between cost and outcomes when survivor-treatment bias was not accounted for. Without addressing this form of time-dependent bias, which has traditionally been overlooked, it is possible that patient-level research will unintentionally overstate the importance of AMI costs in relation to survival outcomes. This work may point to survivor-treatment selection bias as a significant source of bias in health care cost-outcomes research for other disease conditions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.

Appendix SA2: Data Layout Sample Using the Counting Process in SAS 9.2.