The Parametric G-Formula to Compare the effectiveness of Two Anemia Management Strategies Among Medicare Dialysis Patients

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Abstract

Background. Conventional statistical approaches for observational studies are not well-equipped to deal with dynamic treatment strategies primarily due to time-dependent confounding. The parametric g-formula can appropriately adjust for this type of confounding. However, its use and feasibility based on claims data are unknown.

Objective. To assess the feasibility of applying the g-formula approach to large claims data.

Methods. We implemented and adapted the parametric g-formula to compare the risks and benefits of targeting two hematocrit (Hct) levels (high vs. low) among Medicare dialysis patients. For validation, using observational data from the US Renal Data System, we emulated Normal Hematocrit Study (NHS), an existing randomized trial that compared normal verses low strategies, and evaluated statistical efficiency and validity of estimates.

Results. Preliminary results indicated that the estimates obtained from the g-formula were similar to those reported in the NHS and also to those based in inverse probability (IP) weighting approach. Specifically, using the parametric g-formula and IP-weighting methods, we estimated that risk ratio at the end of study follow up for the high-Hct grup as compared with low-Hct group was 1.17 and 1.21, respectively. Results were robust to assumptions about missing Hct and extent of modeled treatment history.

Conclusion: The parametric g-formula is a feasible technique to compare dynamic treatment strategies using claims data within a framework in which this method can be generalized for a broader causal inference questions.

Key Words: Causal Inference, G-formula, Claims data, Inverse probability weighting, Dynamic treatment strategies, Time-dependent confounding

1. Introduction

Key questions in patient-centered outcomes research (PCOR) involve dynamic treatment strategies for persons with chronic medical conditions. A dynamic treatment strategy is a set of rules for assigning treatment to individual patients based on that individual's evolving characteristics and response to prior treatment, with the goal of optimizing the long-term clinical outcome.[1] For example, patients with chronic kidney disease are given epoetin for the correction of their anemia. At repeated visits, hematocrit and other covariates are observed and the epoetin dose is adjusted accordingly to reach the desired hematocrit target. While randomized trials remain the gold standard for determining the effects of varying interventions on patient outcomes, they usually compare nondynamic treatments, and in many situations are not feasible, ethical, or timely. In contrast,

conventional statistical approaches for observational studies are not well-equipped to deal with dynamic strategies due to bias.[2,3] Two advanced approaches for the comparison of dynamic strategies are inverse probability (IP) weighting [4,5] and the parametric g-formula, [6,7] both of which are superior to conventional methods because they appropriately adjust for measured time-varying confounders. However, the g-formula method has never been applied to large administrative database. Therefore, its feasibility and relative advantages and disadvantages to comparing dynamic treatment strategies using administrative data is unknown.

The goal of this PCORI-funded PILOT project is to assess the feasibility of applying the g-formula and IP weighting to claims data by implementing and validating these two methods. We propose to use, as a case study, the comparison of dynamic strategies for epoetin to treat anemia among dialysis patients covered by Medicare. The issues in prescribing epoetin are similar to those found in many chronic conditions: a treatment whose duration and dose changes in response to time-varying prognostic factors that are themselves affected by prior treatment.

2. Case study: Evaluation of EPOETIN Treatment Strategies Among Medicare Dialysis patients

2.1. Methods

In this case study, we used observational data from the United States Renal Data System (USRDS) to emulate a randomized clinical trial (Normal Hematocrit Study, NHS)[8] among elderly patients with clinical evidence of congestive heart failure (CHF) or ischemic heart disease (IHD) who were undergoing hemodialysis (**Table 1**). The USRDS includes 93% of U.S. dialysis patients with Medicare coverage.[9] Most claims cover a service period of approximately one month (average duration is 24 days).[10] We used the USRDS standard analytic files for 2006-2011 that contained variables from patient, medical evidence, and facility data files. **Figure 1** represents the patient selection process.

We considered two dynamic treatment strategies for epoetin use:

1. *High Hct Strategy*: intravenous epoetin alfa to achieve and maintain hematocrit values between 36.0 and 42.0% or
2. *Low Hct Strategy*: intravenous epoetin alfa to achieve and maintain hematocrit values between 30.0 and 36.0%.

During the first month of follow up, initial treatment strategy is defined based on the following rules:

- High-Hct group: dose is increased by a factor of 1.15
- Low-Hct group: dose is adjusted at ± 15%.

During subsequent months,

In IP-weighting analysis: treatment strategies are repeatedly evaluated based on the following rules:

i. Increase dose if Hct is below the lower end of the target range;
ii. Decrease dose if Hct is above the higher end of the target range;
iii. Adjust dose at ± 15% of previous dose if Hct is between.

Patients are artificially censored when they stop following their originally assigned strategy, defined as the 2nd time that a deviation happens.

In the g-formula analysis: Deterministic threshold interventions of High-Hct strategy vs. Low-Hct strategy are defined as follows:

i. If Hct < lower end of target and dose <previous dose then set dose to

1.25*previous dose;

ii. If Hct > higher end of target and dose>previous dose then set dose to 0.90*previous dose;

iii. If Hct between lower and higher of target then set dose to previous dose.

For simplicity we did not consider strategies that vary according to the evolving clinical characteristics of the patients. Similar to NHS trial, the two endpoints of interest were all-cause mortality and a composite outcome including death and hospitalization for myocardial infarction (MI), stroke, or congestive heart failure (CHF).**Error! Bookmark not defined.**, **Error! Bookmark not defined.** Previous studies have verified that ICD-9 codes used to define MI, CHF, and stroke have specificity higher than 90% and sensitivity between 67% and 86%.[11,12,13,14]

Table 1 below summarizes the characteristics of NHS trial and how we emulated it using the observational data.

Table 1: Replication of NHS RCT using USRDS observational data.*

Component	NHS (randomized, open-label, non placebo trial)	Emulated trial using USRDS observational data
Aim	To compare the risks and benefits of targeting a hematocrit (Hct) 42% ± 3 % versus 30% ± 3%.	To compare the risks and benefits of targeting a hematocrit (Hct) 39% ± 3 % versus 33% ± 3%. *Justification* for modification: Cannot use same Hct target as NHS because practically few patients were targeted at Hct >42% or <30% between 2006 and 2010 enrollment period.
Study Population	1. Hemodialysis patients with Hct values of 27-33% who received epoetin during the four weeks before study entry. 2. Enrollment period 1993-1996.	1. Patients who undergoing hemodialysis with Hct values of 30-36% and received Epo therapy in the month prior to study entry 2. Enrollment period 2006-June 2010.
Inclusion Criteria	1. Congestive heart failure (CHF) in 2 years before study entry, or 2. Ischemic heart disease (IHD) in 2 years before study entry and a serum transferrin saturation of 20% or higher at study entry.	Same (identified from Medicare inpatient and/or outpatient claims). Serum transferrin saturation criterion was not applied due to data unavailability in Medicare claims.
Exclusion Criteria	1. Myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary-artery bypass grafting in the 3 months before study entry. 2. Severe cardiac disability 3. Pericardial disease	1. Same, MI identified from inpatient claims based on primary diagnosis for hospitalization in previous 3 months. PTCA and CABG are identified using ICD-9 procedure codes from inpatient claims. 2. Defined as >2 hospital admissions for CHF in previous 6 months 3. Same (based on primary diagnosis for hospitalization) 4. Same (based on primary diagnosis for hospitalization)

	4. Cardiac amyloidosis 5. Androgen therapy 6. Diastolic blood pressure of 100 mm Hg or more; cardiac valvular disease likely to require surgery 7. Life expectancy <6 months	5. Criterion not used because androgen therapy was not used after 1990. 6. Criteria not used. These conditions are uncommon in the cohort. 7. Criterion not used. *Additionally*, potentially non-responders (patients who received dose greater than 700 units/week/kg before study entry) were excluded.
Follow-up	Follow-up started at randomization after all eligibility criteria were met. Follow-up finished at death, loss to follow-up (not defined in the study), 30 months after randomization, whichever occurred earlier (*the study was terminated at 29 months).*	Follow-up starts after all eligibility criteria were met Follow-up finishes at death or Dropout/loss to follow-up defined as the earlier of 1) key data become unreliable, 2) Darbepoetin use, and 3)30-day gap in outpatient dialysis or inpatient claims
Treatments	Patients are randomly assigned to one of the following two treatment groups: 1. Normal-Hct group: intravenous epoetin alfa to achieve and maintain hematocrit values of 39-< 45% or 2. Low-Hct group: intravenous epoetin alfa to achieve and maintain hematocrit values of 27-<33%.	Patients were classified as one of the two groups below: 1. High-Hct group (targeting Hct 36-42%): 25,086 patients identified who met study eligibility criteria. 2. Low-Hct group (targeting Hct 30-36%): 16,041 patients identified who met study eligibility criteria.
Study Protocol	In the normal-Hct group, • the dose was increased by a factor of 1.5 on study entry; • Subsequently, doses were increased by 25% of the base-line dose if the hematocrit had not increased by at least 2 percentage point during the preceding two weeks; • If the Hct increased by > 4 percentage points in a 2-wk period, the dose was reduced by 25 U per kilogram of body weight; • Iron status was evaluated for poor responders. In the low-Hct group, • dose was adjusted by 10 to 25 U/kg at 2-wk intervals, when needed, to maintain a hematocrit of 30%.	*During the first month of follow up*, initial treatment strategy is defined based on the following rules: High-Hct group: dose is increased by a factor of 1.15 Low-Hct group: dose is adjusted at ± 15%. *During subsequent months,* **In IP-weighting analysis:** treatment strategies are repeatedly evaluated based on the following rules: i. Increase dose if Hct is below the lower end of the target range; ii. Decrease dose if Hct is above the higher end of the target range; iii. Adjust dose at ± 15% of previous dose if Hct is between. Patients are *artificially censored* when they stop following their originally assigned strategy, defined as the 2nd time that a deviation happens. **In the g-formula analysis:** Deterministic threshold interventions of High-Hct strategy vs. Low-Hct strategy are defined as follows:

		i. If Hct < lower end of target and dose <previous dose then set dose to 1.25*previous dose; ii. If Hct > higher end of target and dose>previous dose then set dose to 0.90*previous dose; iii. If Hct between lower and higher of target then set dose to previous dose.
Baseline characteristics	Age, gender, duration of dialysis, cause of renal failure, type of vascular access, hypertension, diabetes mellitus, peripheral vascular disease, cardiac-related hsopitalization including angina pectoris, CHF, MI, CABG, and PTCA, New York Association class I, II, and III, hematocrit (%), and epoetin dose (U/kg/wk)	Except for New York Heart Association class which was not available in USRDS data, all other baseline covariates included in NHT were included in our study. Additionally, we include: US geographic region (Northeast [networks 1-5], Southeast [networks 6-8, 13, 14], Midwest [networks 9-12], West [networks 15-18]), dialysis chain membership (five largest chains and small/nonchain facilities).
Time-Varying covariates	Not collected	Included Hct, change in Hct values, hospitalization, epoetin withheld, iron dose, epoetin dose (cubic splines, units per week per kg)
Endpoints	*Primary:* all-cause mortality or a first nonfatal myocardial infarction. *Secondary*: mortality and MI alone, hospitalization, CHF, unstable angina, CABG, PTCA, quality of life, change in cardiovascular drugs, and red-cell transfusion.	*Primary*: Same. *Secondary*: Same with the exception of quality of life and change in cardiovascular drugs, which cannot be measured using USRDS data and were therefore not considered.

***Identification of inclusion and exclusion criteria listed in **Table 1** above.*

Conditions	**Codes**
CHF[15]	ICD-9-CM diagnosis codes 398.91, 422.xx, 425.x, 428.xx, 402.x1, 404.x1, 404.x3, and V42.1
IHD[16] (Atherosclerotic heart disease or ASHD)	ICD-9-CM codes 410 to 414, V45.81, and V45.82
Angina Pectoris	ICD-9 413
Myocardial infarction	ICD-9 410
Percutaneous transluminal coronary angioplasty (PTCA)	ICD-9-CM procedure codes (00.66, 36.01, 36.02, 36.05)[17. 18 19]
Coronary-artery bypass grafting (CABG)	36.1x (ICD-9-CM procedure codes) [17,20]
Pericardial disease (**Pericarditis?)**	ICD-9-CM diagnosis codes 420.0, 420.90, 420.91, 420.99, 423.1, and 423.2
#6. Cardiac amyloidosis[21]	ICD-9-CM 277.3
Blood-transfusion[22]	ICD-9-CM procedure codes 99.0 and 99.04 . CPT-4 code 36430 and HCPCS codes P9010, P9016, P9021, P9022, P9038, and P9040
Hypertension	401-405
Diabetes	250, 357.2, 362.0, and 366.41
Peripheral vascular disease [23]	440-444; 447; 451-453; 557

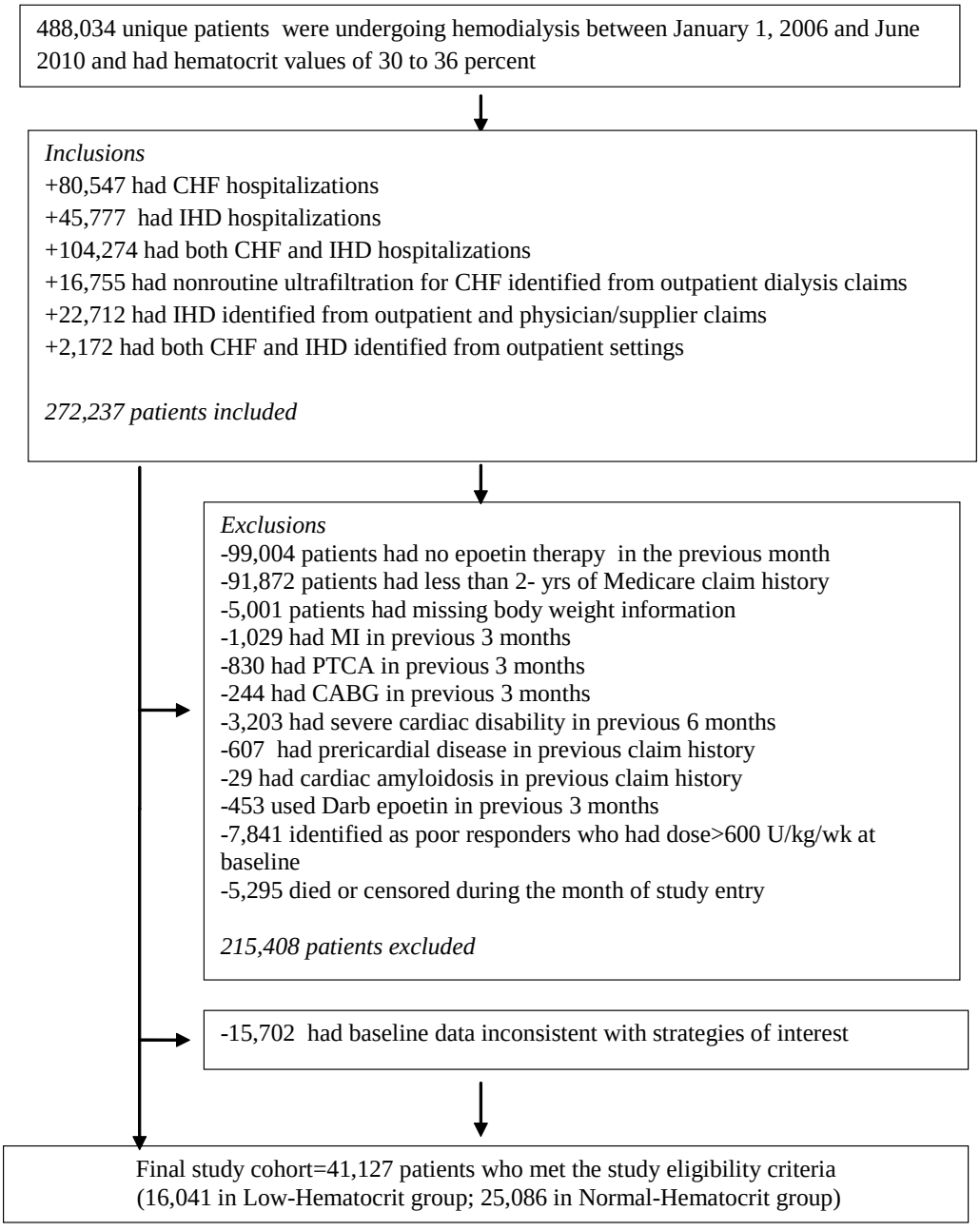


Figure 1. Flowchart of patient selection from USRDS data.

Inverse-probability Weighting analysis

We fit separate pooled logistic models to estimate the probability of death and of the composite outcome at each month, conditional on an indicator for treatment strategy (High or Low Hct), baseline covariates listed in Table 1 above, and month of follow-up (cubic splines). To adjust for potential selection bias due to censoring by loss to follow-up, we estimated stabilized inverse probability (IP) weights as previously described.[24,25,26] The weighted outcome models estimate the observational analog of the intention-to-treat average hazard ratio (HR) for the High Hct vs. Low Hct strategies.

We also conducted the observational analog of a "per-protocol" analysis in which we estimated the effect estimates if all subjects had adhered to their baseline strategy throughout the entire follow-up. To estimate the per-protocol HR of the outcome for Mid Hct vs. Low Hct Strategy, we fit the above models after censoring patients when they deviated from their original strategy. We used stabilized IP weights to adjust for time-dependent selection bias due to this censoring.[27] Calculation of treatment weights was based on the ratio of two predicted probabilities:

- Denominator: predicated probability of observed exposure status (in this case not being artificially censored given confounders and baseline variables
- Numerator: predicted probability of observed exposure status given baseline variables only

Weight at time t was the product of these ratios up to time t. We examined the treatment weights by evaluating and comparing the distribution of Hct and epoetin dose before and after the weighting in both groups (**Table 2a-b,** for endpoint death).

Table 2a. Unweighted per-protocol average HCT (%) and dose during follow-up

Month of follow up	L-Hct (30-36%)			H-Hct (36-42%)		
	HCT		Dose	HCT		Dose
	N	Mean	Mean	N	Mean	Mean
0	16041	34.5	198	25086	33.5	298
1	16041	35.3	200	25086	34.2	314
2	15525	40.9	207	24155	35.8	282
3	13331	37.8	215	19913	36.5	274
4	11330	35.5	221	15467	36.7	284
5	9578	35.5	230	11954	36.2	302
6	8040	36	229	9389	35.9	318
7	6665	35.7	234	7269	35.9	325
8	5518	35.7	245	5718	36.1	319
9	4575	35.9	248	4489	36.1	331
10	3764	36.6	249	3557	36.1	342
11	3136	35.6	254	2831	36.2	327
12	2609	35.8	260	2267	36.2	319
13	2163	35.9	250	1797	36	306
14	1861	35.9	246	1427	35.7	310
15	1585	35.8	239	1151	35.5	321
16	1348	35.7	234	942	35.7	294
17	1149	35.6	238	769	35.8	291
18	969	35.6	229	642	35.8	279

Table 2b. Weighted per-protocol average HCT and dose during follow-up

Month of follow up	Group			
	L-Hct (30-36%)		H-Hct (36-42%)	
	Hct	dose	Hct	dose
	Mean	Mean	Mean	Mean
0	34.5	199	33.5	298
1	35.3	201	34.1	315
2	34.9	209	37	228
3	35.1	214	37.8	224
4	35.1	214	37.7	233
5	35.1	215	37.4	267
6	35.1	208	37.4	276
7	35	213	37.3	290
8	34.9	219	37.5	289
9	34.9	227	37.7	276
10	34.8	229	37.5	323
11	34.4	202	37	306
12	34.9	210	37.7	332
13	35.2	192	37.6	441
14	35.3	187	36.3	385
15	35.1	182	36.5	369
16	35.3	153	36.8	330
17	34.8	151	36.3	300
18	35.2	168	37.2	315

The estimated weights had a 99th and 95th percentile values of 425 and 4 for both study endpoints and mean value of 1.1 (SD 2.5). We also estimated the survival curves under each treatment strategy by using the predicted values of weighted outcome models that additionally included the product ("interaction") terms between the treatment strategy indicator and the month variables. Point-wise 95% confidence intervals for all parameter estimates were calculated via non-parametric bootstrap based on 200 full samples.

The parametric g-formula analysis

The g-formula[5] can consistently estimate the death and MI risk under a hypothetical intervention, under the assumption that all joint predictors of the outcome and of the exposures involved in the intervention are measured at all time points. In this analysis, we implements an SAS macro that have been developed to implement the parametric g-formula available on Harvard University School of Public Health website (http://www.hsph.harvard.edu/causal). Details regarding how we adapted this macro to our case study can be available upon request. Briefly, the algorithm for our application of the parametric g-formula is outlined below :

- Parametric modeling to estimate factors of the g-formula (For each month during the study follow up period, first model on the whole sample the following as a function of prior risk factor history: each risk factor and risk of study outcomes. Baseline and time-varying risk factors were the same to those used in the IP-weighting analysis. Then simulate a cohort for each month under the intervention of interest).
- Monte Carlo simulation to approximate the integral
- Computation of the cumulative risk
- Nonparametric bootstrap for variance estimation

2.2. RESULTS

Patient Characteristics

Table 3 below shows baseline patient characteristics by Hct target groups.

Table 3. Base-line Characteristics of the Patients.*

Characteristic	High-Hematocrit Group (N=25,086)	Low-Hematocrit Group (N=16,041)
Age (yr)	65±14	65±14
Female Sex (%)	47.7	47.3
Race		
White	54.9	57.1
Black	39.1	37.0
Other	6.0	6.0
Duration of dialysis (yr)	5.0±3.5	5.0±3.4
Cause of renal failure (%)		
Diabetes mellitus	49.2	49.1
Hypertension	28.6	29.3
Glomerulonephritis	9.6	9.5
Other	12.6	12.1
Type of vascular access (%)	?	
Hypertension (%)	96.4	95.9
Diabetes mellitus (%)	65.2	64.0
Peripheral vascular disease (%)	43.4	41.1
Cardiac-related hospitalization(%)		
Angina pectoris	11.5	11.8
Congestive heart failure	59.6	56.7
Myocardial infarction	17.6	16.7
Coronary-artery bypass graft	8.4	8.9
Percutaneous transluminal coronary angioplasty	13.0	13.6
Hematocrit (%)	33.5±1.7	34.5±1.4
Epoetin dose (U/kg/wk)	143±124	197±143

*Plue-minus values are means ± SD. Because of rounding, not all percentages total 100.

Results based on IP-weighting analysis

Table 4. Hematocrit target treatment strategies and hazard ratios (HRs) based on intention-to-treat and per-protocol analyses*					
	Patient months	Events			
Intention-to-treat			HR	95% CI	
Death only					
Low Hct (30.0-<36.0%)	213,042	4,313	1 (ref.)		
High Hct (36.0-<42.0%)	325,790	7,275	1.15	1.12	1.18
Composite					
Low Hct (30.0-<36.0%)	208,402	4,702	1 (ref.)		
High Hct (36.0-<42.0%)	318,567	7,859	1.13	1.11	1.15
Per-protocol					
Death only					
Low Hct (30.0-<36.0%)	107,358	2,409	1 (ref.)		
High Hct (36.0-<42.0%)	136,366	3,683	1.18	1.02	1.37
Composite					
Low Hct (30.0-<36.0%)	105,056	2,625	1 (ref.)		
High Hct (36.0-<42.0%)	133,582	3,955	1.18	1.02	1.36
Abbreviation: HR: hazard ratio. CI: confidence interval.					
Composite outcome is death or hospitalization for MI					
*Inverse probability weighted estimates adjusted for age at ESRD onset, race, gender, US geographic region, dialysis chain membership, baseline hematocrit level, epoetin dose, hypertension, diabetes, peripheral vascular disease, and cardiovascular hsopitalizations.					

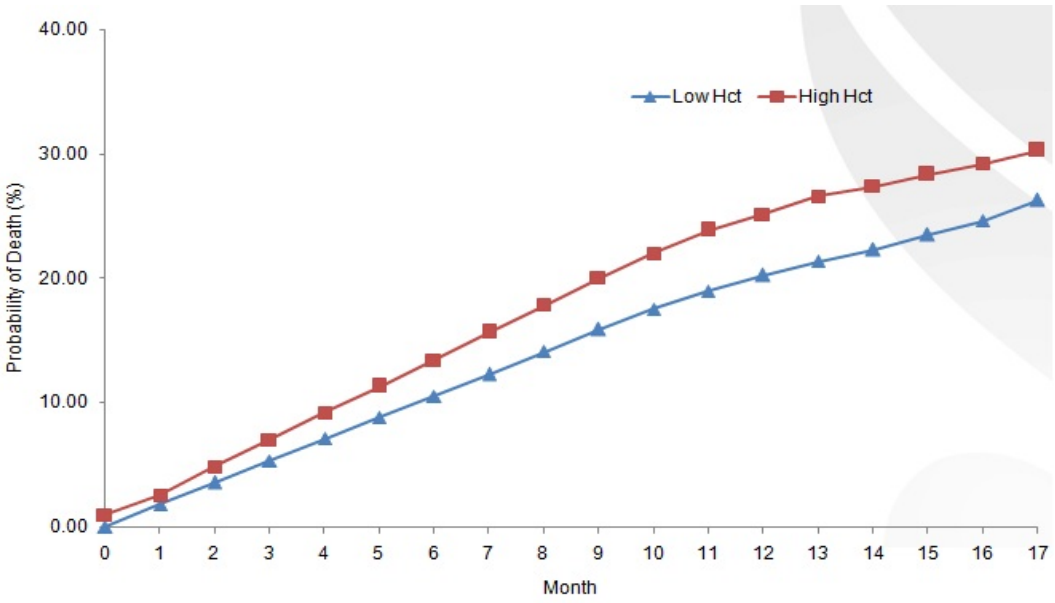


Figure 2. Kaplan-Meier Estimates of the Probability of Death

Results based on the g-formula analysis

Observed cumulative mortality risk=35.2%; cumulative mortality under natural course of epoetin treatment=35.1%. Using natural course (no intervention) as the reference, risk ratios were 1.00 and 1.17 for L-Hct group and H-Hct group, respectively.

Figure 2a . Estimated observed and "natural course" mortality by month.

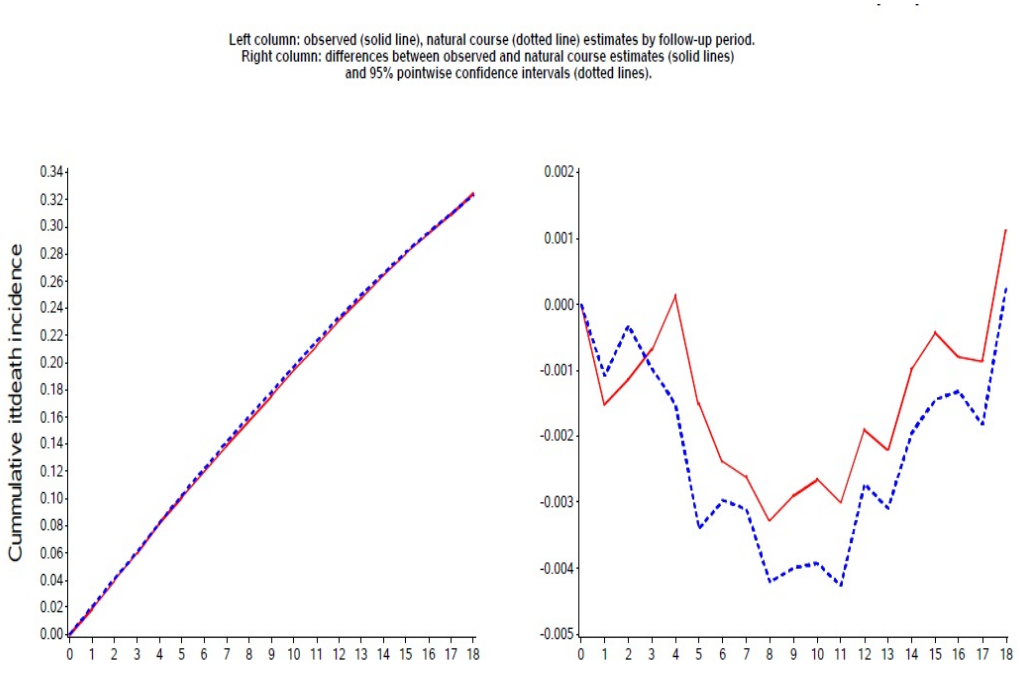


Figure 2b. Estimated observed and simulated mean Hct by month

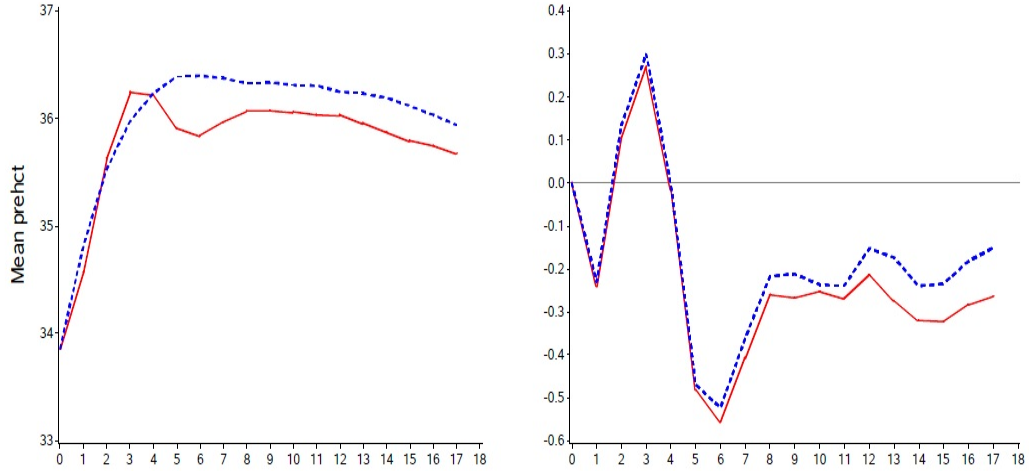
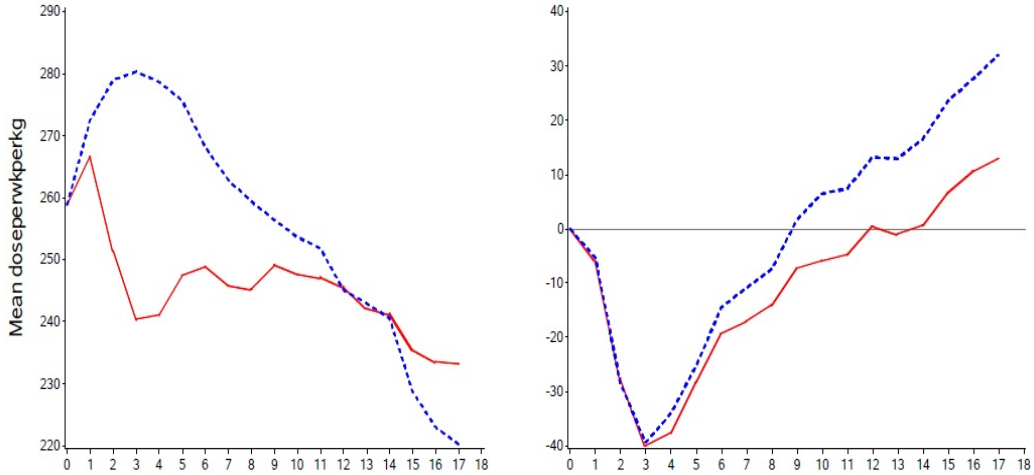


Figure 2c. Estimated observed and simulated mean epotin dose (units/wk/kg) by month



3. Discussion

Commonly used statistical methods (e.g., regression analysis, propensity scores) are based on the estimation of effect estimates within strata of the data defined by the confounders or the propensity score. These stratification-based methods cannot appropriately handle time-dependent confounders that are affected by prior treatment (e.g., intermediate events on the causal pathway between treatment and disease),[28, 29] pervasive in many areas of clinical epidemiology. In the presence of time-dependent confounding, conventional statistical approaches to estimate the causal effect of a treatment regimen will often produce biased results even if all confounders are measured and the regression model is correctly specified.[30] In contrast to standard statistical methods, two approaches for the comparison of dynamic strategies--inverse probability (IP) weighting[31, 32, 33] and the parametric g-formula[34, 35] – have been developed to appropriately adjust for time-dependent confounding. In this first application of the

parametric g-formula approach to Medicare claims data, we have demonstrated that the parametric g-formula provides comparable results to both inverse probability weighting and RCT results. Like standard regression models, the parametric g-formula requires the assumptions of no unmeasured or residual confounding, no measurement error and no model misspecification. Unlike standard methods, the parametric g-formula can deliver consistent estimates of risk even when there exists time-dependent confounding. Below we summarized the pros and cons of the g-formula approach vs. IP-weighting:

Pros:

- Flexible (allow you to define a wide of range of hypothetical interventions, including joint and dynamic ones from complex longitudinal data)
- Multiple hypothetical interventions can be compared at same time.
- SAS macro available to facility its use with complex longitudinal data

Cons

- Defining practically implementable interventions might be a challenge.
- Maybe more sensitive to violations of unmeasured confounding assumptions
- Biases associated with potential model misspecifications.

4. Conclusions

The parametric g-formula is a feasible and an alternative way for causal inference based on the complex longitudinal data. Given the available of SAS G-formula macro, the parametric g-formula should be routinely used for analysis of dynamic treatment regimens together with the IP-weighting approach

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DISCLAIMER:

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.The data reported herein have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as the official policy or interpretation of the US government.

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