Supplemental Materials for Online Archive

Title: A Within-Patient Analysis for Time-varying Risk Factors of CKD Progression

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Statistical Details

From a statistical perspective, there are two kinds of time-varying risk factors in this paper: binary and continuous. The first metric in the *hospitalization* category is binary (Table 2), and all others are continuous variables. For a binary time-varying risk factor, we used McNemar test for the unadjusted comparison, and used the following conditional logistic regression for the adjusted analysis:

$$\log it\left(Y_{ij} = 1\right) = \beta_0 + \beta_1 S_{ij} + \beta_2 Z_{ij} + \beta_3 W_{ij} + \alpha_i + \varepsilon_{ij},$$

where $i = 1,2,...,74$ is the index of the 74 patients in this analysis, and $j = 1,2$ index the early and late period. S_{ij} is an indicator that equals 0 if the j th period of patient i is a decline period and equals 1 if it is a stable period. Z_{ij} equals 0 if the period is an early period, and equals 1 if the period is a late period (i.e., $Z_{ij} = j - 1$). W_{ij} equals the mean eGFR of the j th period of patient i, as identified from the estimated trajectory. α_i is a patient-specific random intercept with mean zero that introduces within-patient correlation to Y. In this model, β_1, β_2 and β_3 quantify the odds ratios of the stable period, the late period, and the mean eGFR, respectively.

For a continuous time-varying risk factor, we used paired t-test for unadjusted analysis, and used the following linear model for the adjusted analysis:

$$Y_{ij} = \beta_0 + \beta_1 S_{ij} + \beta_2 Z_{ij} + \beta_3 W_{ij} + \alpha_i + \varepsilon_{ij}.$$

The syntax is similar to the conditional logistic regression model above, except that ε_{ij} is an independent residual noise term with mean zero. In this model, β_1, β_2 and β_3 quantify the effects of the stable period, the late period, and the mean eGFR, respectively, on the mean of Y. The model above implies that

$$Y_{i2} - Y_{i1} = \beta_1 \left(S_{i2} - S_{i1} \right) + \beta_2 \left(Z_{i2} - Z_{i1} \right) + \beta_3 \left(W_{i2} - W_{i1} \right) + \left(\varepsilon_{i2} - \varepsilon_{i1} \right) ,$$

which is a linear model without intercept and can be fit using standard software for linear models. We made no assumptions on the distributions of α and ε terms beyond zero mean, and used the sandwich method to derive the variance estimator in anticipation of some heterogeneity in the variance of $\varepsilon_{i2} - \varepsilon_{i1}$.

All analyses above were performed using R 2.12.2 (www.r-project.org). For statistical tests, the α level of 0.05 was used.

Table A1. Number of hospitalization episodes with the primary or secondary ICD-9 diagnosis codes

ICD-9 code	Composite ICD-9 code: either primary or secondary		Primary ICD-9 code		Secondary ICD-9 code	
	Decline periods	Stable periods	Decline periods	Stable periods	Decline periods	Stable periods
Cancer	6	2	5	2	2	0
Cardiovascular	19	12	16	9	9	6
Endocrine	4	0	3	0	1	0
Fluid	1	2	1	0	0	2
Hypertension	8	13	4	11	4	2
Infection	2	3	2	3	0	1
Other	12	17	10	10	3	10
Psychiatry	1	2	0	2	1	1
Pulmonary	2	1	1	0	1	1
Renal	1	1	1	1	0	0
Surgery	16	2	7	2	9	0
None	20	17	0	0	20	17

Table A2. Comparison of the average percentage of time that a patient is on a medication between the stable and decline periods. The unadjusted or adjusted mean differences are expressed as the estimator (standard error)

	Unadjusted comparison				Adjust for early/late and mean eGFR	
Medication	Mean of stable periods	Mean of decline periods	Unadjusted mean difference (stable – decline)	p-value	Adjusted mean difference (stable – decline)	p-value
ACE/ARB	67.1	71.3	-4.1(7.5)	0.58	6(5.7)	0.25
Acetaminophen	15.1	14.5	0.6(3.5)	0.87	3.2(3.4)	0.32
Alpha-1 Adrenergic Agent	42.5	46.1	-3.6(5.4)	0.51	-7.9(5.2)	0.12
Aminoglycoside	0.3	0.04	0.23 (0.27)	0.39	0.09(0.3)	0.56
Antiplatelet aspirin	18.9	21.7	-2.8(4.2)	0.50	-1.9(4.3)	0.63
Beta Blockers	41.4	47.6	-6.2 (6.2)	0.31	-2.8(6.2)	0.66
Central Adrenergic Agent	34.4	35.1	-0.7(4.6)	0.87	-0.5(4.8)	0.91
Di-hydropyridine Calcium Channel Blocker	31.3	37.1	-5.8(5.3)	0.27	-0.9(5.0)	0.86
Non-Di-Hydropyridine Calcium Channel Blocker	7.0	13.1	-6.2(4.0)	0.12	-4.3(3.9)	0.24
Distal Diuretic	15.4	17.6	-2.3(3.6)	0.52	-2.3(3.6)	0.52
Gout	29.7	27.4	2.3(3.7)	0.53	5.1(3.6)	0.20
HMG CoA Inhibitors	23.8	25.7	-1.9(6.1)	0.76	4.4(5.6)	0.44
Potassium-Sparing Diuretic	7.7	8.5	-0.9(2.7)	0.75	0.68(2.7)	0.81
Loop Diuretic	79.6	78.9	0.7(4.0)	0.87	2.9(4.1)	0.49
NSAID	7.0	7.8	-0.7(2.2)	0.74	-0.87(2.3)	0.74
Vasodilator	26.2	21	5.2(4.2)	0.21	2.9(4.2)	0.46
Miscellaneous	12.2	11.2	1.0(4.4)	0.82	1.7(4.6)	0.73
Mineral Supplements						
Iron (Fe)	6.9	10.6	-3.8(2.7)	0.16	-2.5(2.7)	0.40
Potassium (K)	26.5	28.8	-2.4(3.5)	0.49	-2.3(3.6)	0.51