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Commentary: Enhancing risk assessment by incorporating more of what we know

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Supplemental material is available online.

The closest preoperative values of variables to time of surgery almost exclusively populate risk assessment models, with the notable exception of time since most recent acute myocardial infarction.¹ In their article in this issue of the *Journal*, Griffin and colleagues² remind us that the degree of organ function deterioration may be a more powerful risk factor than traditional preoperative values. In this commentary, we consider 6 features of preoperative variables that can be incorporated into multivariable models and provide computer code (Appendix E1) and mathematical (Appendix E2) descriptions.

FEATURE 1: SINGLE VALUES REFLECTING PREOPERATIVE PATIENT/ORGAN STATUS

These “baseline” values are implicitly assumed to be static and, if continuous, measured without error. They are incorporated straightforwardly as covariates in multivariable models.

FEATURE 2: AVERAGE OF MULTIPLE (>1) MEASUREMENTS OF SAME PREOPERATIVE VARIABLE

This is typical of echocardiographic measurements in which values from 3 or more heartbeats are averaged.

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Individual creatinine trajectories for discovery of effect on post-transplantation survival.

CENTRAL MESSAGE

Although preoperative baseline values predominate risk assessment models, other features of a patient's state, such as rapidity of renal function deterioration, may be even more informative.

The average is the covariate entered into the multivariable models. Information lost by this is beat-to-beat variability.

FEATURE 3: AREA UNDER A “CURVE” OF MULTIPLE VALUES

This is a refined version of feature 2, in that a variable such as atrial fibrillation is observed multiple times across time (as might become commonplace with wearables) to provide information about disease burden over a designated period.³ This feature can be estimated directly from the longitudinal sequence of preoperative measures or from a fitted temporal trend (smoothed version of raw data⁴) using integration.

FEATURE 4: VALUES BASED ON CLINICAL CRITERIA

This is what Griffin and colleagues have presented, in which 2 values were measured, the first being the lowest creatinine value measured in the 3 months before surgery and the second being the measurement immediately before surgery.² They entered the difference between these 2 measurements into their multivariable model. (Note that use of “change scores” like this has important statistical drawbacks.^{5,6}) Because measurements cannot be made continuously, it is unknown what the lowest creatinine value was in that 3-month interval.

FIGURE 1. Importance of recording time of preoperative measurements. Illustrated are values for some preoperative variables, such as creatinine, for 2 patients (*blue and red lines*) who have the same minimum value and an immediate preoperative measurement. Considering just the difference between these 2 measurements as in Griffin and colleagues² produces the same value (see feature 2). However, 1 patient had a more gradual increase over a longer time (lower slope), as shown in *blue*, than the other patient with the same increase, but over a shorter time interval (steeper slope). These different slopes may have different effects on the outcome (Response Y), despite the identical immediate preoperative value.

FEATURE 5: INDIVIDUAL PATIENT SLOPES OF VALUES

This feature is what is missing from the article: a temporal slope of preoperative creatinine. Had timing of the measurements been known, an approximation of the slope could have been estimated and used in their analysis (Figure 1).

FEATURE 6: TEMPORAL PATIENT-SPECIFIC TRAJECTORY OF VALUES

Feature 6 is more advanced than feature 5, incorporating all observed longitudinal measurements (>2), or smoothed version thereof, and time of measurement (Figure 2)

directly into the multivariable outcomes model, a time-varying coefficient model.⁷ Smoothed values can be obtained by linear or nonlinear mixed-effects parametric models⁸ or by a nonparametric approach.⁴

CONCLUSIONS

All these features can be implemented in 2 steps using readily available software. Step 1 is estimating the feature, and step 2 is using the feature as a covariate in multivariable models of outcomes. For features 5 and 6, these 2 steps can be accomplished simultaneously by joint modeling.⁹

Incorporating such features could, as Griffin and colleagues state, enhance risk models and “trigger heightened vigilance in the postoperative period.”²

FIGURE 2. Effect of repeated measurements of pretransplantation renal function on survival after heart transplantation. Each line depicts an observed patient-specific longitudinal profile of pretransplantation creatinine over the 6 months before transplantation.

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Commentary: Absolute creatinine values and preoperative acute kidney injury in cardiac surgery patients: Are we barking up the wrong tree?

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Acute kidney injury (AKI) has been shown to occur in up to 22.3% of patients following cardiac surgery.¹ Multiple studies have demonstrated that pre- and post-operative AKI is associated with poor postoperative outcomes.¹⁻³ Previously, Hobson and colleagues² demonstrated that postoperative AKI was an independent predictor of mortality (hazard ratio, 1.39, 95% confidence interval [CI], 1.23-1.57). In a large database study, Cooper and colleagues³ found that declining preoperative estimated glomerular filtration rate was associated with increased operative mortality and increased postoperative AKI

Carly Lodewyks, MD, MSc, and Rakesh C. Arora, MD, PhD

CENTRAL MESSAGE

AKI is an important cause of morbidity and mortality after cardiac surgery. Small changes in preoperative creatinine from baseline may also be harmful; however, the accuracy of this needs to be confirmed in future studies.

requiring dialysis, stroke, infection, prolonged ventilation, and hospital length of stay.

Until recently, the effect of preoperative kidney disease on postoperative outcomes has been investigated using an absolute creatinine value or single calculated estimated glomerular filtration rate. Griffin and colleagues⁴ sought to determine whether an acute change in preoperative creatinine from a baseline value would significantly influence postoperative outcomes in cardiac surgery patients. In this retrospective study of 1486 patients undergoing nonemergency cardiac surgery, a creatinine change from baseline (minimum creatinine available 3 months after surgery) to the presurgical value was calculated. They observed an

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APPENDIX E1. SAS CODE FOR FEATURE 5

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Two-Step Approach

Step 1: Linear mixed-effects model for longitudinal preoperative measures

Step 2: Cox proportional hazards model for time to event, where patient-specific slopes, which are estimated using a linear mixed-effects model in step 1, are entered as a covariate in the time-to-event model.

Dataset – Built: Multiple record dataset

*****Variables *****

ptid – patient ID
iv_test – time to a preoperative blood testing
creat_pr – preoperative longitudinal measurement of creatinine level
event – (indicator) time to event after time zero (time of surgery)

iv_event – time to the event or censoring

X – other baseline covariates

*****Step 1: Linear Mixed-Effects Model *****

```
proc sort data=built; by ptid iv_test; run;
ods trace on;
ods output parameterestimates=est.peML_avmnr2pt_ab;
proc nlmixed data=built gconv=1E-8 qpoints=1;
parms /**Starting values */
/* overall intercept and slope*/
a0=-0.1346 b1=0.0721
/* Normal model variance for the response */
logsig=-0.325
/* Random effects variance (for intercept and slope)*/
logsigu=-0.5822 logsigv=-1.7407 suv=0.02201
;
l_eta= (a0+u) + (b1+v)*iv_test;
model creat_pr ~ normal(l_eta, exp(2*logsig) );
random u v ~normal([0,0], [exp(2*logsig), suv, exp(2*logsigv)]) subject=ptid out=rand_out;
run; ods trace off;
```

/* Extract estimated patient-specific slopes */

```
data randbi; set rand_out; where Effect='v';
keep ptid estimate b1;
rename estimate=b1i;
data randbi; set randbi; beta_i=(b1i + b1); run;
```

/**Merge with original data */

```
proc sql;
create table built_b as select * from built
as left join randbi
on built.ptid=randbi.ptid;
quit;
```

*****Step 2: Cox PH regression - Response model****

```
Proc phreg data=built_bi;
model iv_event*event= beta_i x1 x2 x3 /* can
include other covariates */
```

Run;

Joint Model Approach

This code is for joint modeling using a linear mixed-effects model for the longitudinal preoperative measures and a Cox-type proportional hazards model for the time to event. Patient-specific slopes are estimated using the linear mixed-effects model and used as a covariate in the time-to-event model. Note that this code fits the 2 models simultaneously. If each patient has sufficient preoperative longitudinal data, the models can be fitted in 2 steps as described above.

Dataset – Built: Multiple record dataset

*****Variables *****

ptid – patient ID
iv_test – time to a preoperative blood testing
creat_pr – preoperative longitudinal measurement of creatinine level
event – (indicator) time to event after time zero (time of surgery)

iv_event – time to the event or censoring

X – other baseline covariates

proc sort data=built; by ptid iv_test; run;

proc nlmixed data=built gconv=1E-8 qpoints=1;

parms /* Starting values*/

/*Longitudinal Data – overall intercept and slope**/

a0=-0.1353 b1=0.072

/* Normal model variance –normality assumption of preoperative measure*/

logsig=-0.324

/* Random effects variance (random intercept and random slope)*/

logsigu=-0.5806 logsigv=-1.7395 suv=0.02139

/* Time to Event : data *****/

/* Late Increasing hazard*/

thalf11=3.2264 nu1=-0.2997

/* covariate in the time to event model */

s1=0.1 l1=-1.2872 l2=0.01760

;

*****Longitudinal data: Likelihood*****

/* Linear mixed effects model*/

l_eta= (a0+u) + (b1+v)*iv_test;

resid = (creat_pr - l_eta);

sigmasq =exp(2*logsig);

```

if (abs(resid) > 1.3E100) or (sigmasq < 1E-12) then
  do;
  llvar = -1e20;
end; else do;
  llvar = -0.5*(1.837876 + resid**2 / sigmasq +
    log(sigmasq) );
  end;
/*****Time to event: likelihood*****/
/*****Time to event: likelihood*****/
if (last) then do;
  /* Late increasing hazard*/
  mul=exp(s1*v +l1*x1 +l2*x2 ....can include other
    covariate in the response model);
/*See Reference 8 for details of baseline parametric
hazard function*/
  thalf1=exp(thalf1l); m1=0;
  %decompos(_complet=1, _time=iv_expl,
    _thalf=thalf1, _nu=nu1, _m=m1);
  haz=mul*_hazard; cumhaz=mul*_cumhaz;
  /* Likelihood */
  llsurv=event*log(haz) - cumhaz;
end; else llsurv=0;
  model z ~ general(llvar + llurv);
  random u v ~normal([0,0], [exp(2*logsigu), suv,
    exp(2*logsigv)]) subject=ptid out=rand_out;

run;
ods trace off;

```

APPENDIX E2: APPENDIX E2. MATHEMATICAL DISCUSSION

Amol Pande, PhD

This Appendix presents various strategies for incorporating preoperative information to assess its association with postoperative events using formal mathematical notation.

Setup

For the i th patient, where $i = 1, 2, \dots, n$, let T_i represent event or censored time, and let $x_i^{(k)}$, for $k = 1, 2, \dots, P$, represent preoperative information that does not vary with time.

A preoperative variable that stands out in the work of Griffin and colleagues^{E1} is preoperative creatinine. We use z_i , for $i = 1, 2, \dots, n$, to denote this variable. In the study of Griffin and colleagues, each patient had at least 2 creatinine measurements of z_i , and the authors took the difference between the lowest and immediate preoperative values. For the purpose of this Appendix, we assume that there could be a single measurement or multiple measurements of the preoperative variable per patient, that is, $z_i = (z_{i,1}, z_{i,2}, \dots, z_{i,n_i})$, and although not measured by Griffin and colleagues, we assume that for multiple measurements of z_i per patient, there is an accompanying variable denoted

by u_i , for $i = 1, 2, \dots, n$. For example, u_i could be the time at which the measurement was made or an increasing index at which z_i is collected.

Model

For the purpose of this Appendix, we use the Cox proportional hazards model for the outcome as a time-related event. This model assumes that the hazard function has the following form:

$$h(t | x_i^{(1)}, \dots, x_i^{(P)}, z_i, u_i) = h_0(t) \exp \left(f(x_i^{(1)}, \dots, x_i^{(P)}, z_i, u_i) \right),$$

for $i = 1, 2, \dots, n$,

where $h_0(t)$ is a baseline hazard function, and $f(\cdot)$ is either an unknown function estimated from the data or, in most cases, the user-specified linear function. Note that if the information for u_i is not available, it can be suppressed in this model.

Strategies for Incorporating Preoperative Information

Here we provide strategies for incorporating z_i (and u_i , if available) in the above model. We assume a linear functional form for $f(\cdot)$, although it can be generalized to account for nonlinearities, and even interactions, among variables.

Feature 1: Each patient has a single measurement of z_i , and the measurement of u_i is not available. The linear functional form of $f(\cdot)$ can be written as

$$f(x_i^{(1)}, \dots, x_i^{(P)}, z_i) = \sum_{k=1}^P x_i^{(k)} b_k + z_i b,$$

where $b_1, \dots, b_P$, and b are unknown parameters that are estimated from the data. The Cox parameter estimation procedure has been described previously.^{E2}

Feature 2: Patients have multiple measurements of z_i but no measurements of u_i . Multiple measurements of z_i are averaged, denoted by $\bar{z}_i$, for $i = 1, 2, \dots, n$. The estimate of $\bar{z}_i$ will be more stable (ie, lower variance) than using any one of the measurements $z_{i,1}, z_{i,2}, \dots, z_{i,n_i}$. The functional form of $f(\cdot)$ can be written as

$$f(x_i^{(1)}, \dots, x_i^{(P)}, \bar{z}_i) = \sum_{k=1}^P x_i^{(k)} b_k + \bar{z}_i b.$$

Feature 4: Each patient has at least 2 measurements of z_i , but the measurements of u_i are not available. Instead of average, the difference between the lowest value and the immediate preoperative value is used—a strategy used by Griffin and colleagues.^{E1} Thus, we use $z_i^* = z_{i,im} - \min(z_{i,1}, z_{i,2}, \dots, z_{i,n_i})$ for $i = 1, 2, \dots, n$, where $z_{i,im}$ is the immediate preoperative value for the i th patient. The functional form of $f(\cdot)$ can be written as

$$f(x_i^{(1)}, \dots, x_i^{(P)}, z_i^*) = \sum_{k=1}^P x_i^{(k)} b_k + z_i^* b.$$

Parameter b provides an association of the preoperative creatinine difference with posttransplantation survival.

Owing to a lack of time measurements, parameter b fails to identify patients with similar preoperative creatinine differences that are measured at different times. We address this in features 5 and 6.

Feature 5: A patient can have a single measurement or multiple measurements of z_i , and the corresponding measurements of u_i are available. We incorporate n_i measurements of z_i and u_i , where $n_i \geq 1$, using the following linear random-effects model to extract the random slope for each patient:

$$z_i = \alpha_i + \beta_i u_i + e_i, \text{ for } i = 1, 2, \dots, n,$$

where α_i and β_i , respectively, represent the random intercept and the random slope. This model provides an estimate of β_i for each patient, which we use in $f(\cdot)$ as follows:

$$f(x_i^{(1)}, \dots, x_i^{(P)}, \beta_i) = \sum_{k=1}^P x_i^{(k)} b_k + \beta_i b_{\text{slope}},$$

where b_{slope} is the regression parameter for the random slope. The random slope represents the patient-specific rate at which preoperative creatinine changes with time. The 2 models described here can be fitted using a 2-step approach or the slightly more complicated joint model approach described in [Appendix E1](#).

Feature 6: The models considered in the preceding text are limited in terms of capability of capturing any nonlinear

relationship of association. A nonlinear relationship can be obtained by considering the following model. To incorporate n_i measurements of z_i and u_i , where $n_i \geq 1$, we need to modify the dimensions of $x_i^{(k)}$, for $k = 1, \dots, P$, so that all variables have the same dimensions; this should be reflected in the dimension of $f(\cdot)$. To do this, we replicate values of $x_i^{(k)}$ n_i times and form a vector $X_i^{(k)}$ of n_i dimension. The functional form of $f(\cdot)$, now in n_i dimension, can be written as

$$f(\tilde{X}_i^{(1)}, \dots, \tilde{X}_i^{(P)}, \tilde{Z}_i, u_i) = \sum_{k=1}^P \tilde{X}_i^{(k)} b_k \mathbf{1} + \tilde{Z}_i b(u_i),$$

where $\tilde{X}_i^{(k)}$ and $\tilde{Z}_i$ are diagonal matrix forms of $X_i^{(k)}$ and z_i , respectively, for $k = 1, 2, \dots, P$, $\mathbf{1}$ is a vector of n_i dimension, and $b(u_i)$ is a function of u_i , which is different from parameter b that we considered earlier. This model is referred to as a varying coefficient model.^{E3} Once the function $b(u_i)$ is estimated, the plot of u_i versus $b(u_i)$ can illustrate possibly hidden trends not revealed in the linear model.

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