Critical Review Form

Clinical Prediction or Decision Rule

Impact of Nephropathy after Percutaneous Coronary Intervention and a Method for Risk Stratification, *Am J Cardiol* 2004; 93:1515-1519

Objective: **To develop a time-insensitive clinical tool able to prospectively risk stratify patients for the development of RCIN (radio-contrast induced nephropathy) after PCI (percutaneous intervention), irrespective of the need for dialysis, and to evaluate the prognostic implications from the development of nephropathy." (p. 1515)**

Methods: **Using a database of William Beaumont Hospital (Royal Oak, MI) cardiac cath patients from 1993 to 2002, excluding those on dialysis (n = 356) or having in-hospital CABG (n = 334), the investigators formed derivation (patients from 1993 to 1998) and validation (1999 to 2002) cohorts. Baseline and peak serum creatinine were recorded for each case. If an individual patient had >1 PCI (n = 10162) then the episode associated with CIN was used in this analysis.**

From > 50 (unnamed) demographic, clinical and procedural characteristics, predictors for CIN were tested in univariate analysis. CIN was the dependent variable and was defined as serum creatine ≥ 1.0 mg/dl above the baseline. Stepwise multivariate regression analysis (of all 50 variables regardless of statistical significance on univariate analysis?) was performed until only variables with p < 0.0001 remained. A propensity score was used to assess whether the multivariate model over fit the data, but investigators do not report which prognostic variables were used in the propensity score.

Creatinine clearance was computed using Cockcroft and Gault. Renal dysfunction was classified according to National Kidney Foundation parameters using GFR: ≥ 90ml/min as "normal"; 60-89 ml/min as "mildly impaired"; <60 ml/min as "at least moderately impaired". Myocardial infarction required at least two of the following: prolonged chest pain; EKG changes, and > 3 fold increase in creatinine kinase. Secondary outcomes included death, MI, or re-occlusion.

Guide		Comments
I.	**Is this a newly derived instrument (level IV)?**	
A.	Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).	No, validated on separate set of patients. Albeit from the same locale. Therefore, a Level III CDR.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	

1a	Were all important predictors included in the derivation process?	Uncertain. The investigators state that "Predictors of nephropathy after PCI were derived from > 50 demographic, clinically, and procedural characteristics in the derivation cohort." (p. 1516) However, they fail to list or reference these risk factors so readers cannot judge whether the original list was all-inclusive (meds? Prior CIN?)
1b	Were all important predictors present in significant proportion of the study population?	Yes. Table 1 (p. 1516) demonstrates the prevalence of each risk factor in the derivation and validation cohorts. Only 3% had an intra-aortic balloon pump and only 3% had thrombolytics used. On the high end 68% had HTN and in the validation cohort 73% had stents.
1c	Does the rule make clinical sense?	Yes, the 8-item rule is very similar to the PGY-I CDR and each component has theoretical rationale for association with CIN.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	Validation on a distinct subset of patients from the same institution. Therefore, a Level III CDR.
3	How well did the validation study meet the following criteria?	
3a	Did the patients represent a wide spectrum of severity of disease?	Uncertain. The authors do not report on the severity of CIN for patients.
3b	Was there a blinded assessment of the gold standard?	No. The investigators do not explain who obtained the serum creatinine levels or whether those individuals were limited to the study objectives of ancillary patient data. Likewise, the investigators provide no details on who ascertained presence or absence of cardiac adverse outcomes or when (how long after PCI) those judgments were made.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	No, the predictor variables were not prospectively defined and the score was not computed by clinicians during the actual patient encounters.

<table>
<tr><td>3d</td><td>Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?</td><td>Probably not. Presumably all patients had creatinine levels checked post-PCI by protocol, but investigators do not state this fact.</td></tr>
<tr><td>4</td><td>How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?

<u>Risk Factor</u> — <u>Score</u>
Creatinine clearance <60 ml/min — 2
IABP — 2
Urgent/emergency PCI — 2
DM — 1
CHF — 1
HTN — 1
PVD — 1
Contrast >260 ml — 1

Interpretation

0-4 = 0.2% risk CIN, 0.2% risk death
5-6 = 2.8% risk CIN, 2% risk death
7-8 = 10% risk CIN, 9% risk death
>9 = 28% risk CIN, 17% risk death</td><td>• The study population was 20,479 and the incidence of CIN was 2% (407/20479) with a trend downward 2.8% from 1993-1998 and 1.2% from 1999 to 2002 (p < 0.0001).
• In patients with CIN the mean increase in creatinine was 2.3 mg/dl.
• No patient with a risk score of <u>≤</u> 1 developed CIN.
• The Hosner-Lemeshow test showed goodness of fit (p = .010)
• The c-statistic was 0.89
• Patients developing CIN were 15-times more likely to have an extended (74 days) hospitalization.
• CIN was associated with significantly increased rates of MI, target vessel reocclusion and combined major adverse cardiac events.</td></tr>
<tr><td>III.</td><td>Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:</td><td></td></tr>
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1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	There have been no impact factor analyses performed for this instrument. Therefore, we are not sure if clinicians would (a) use the instrument; (b) accurately and reliably interpret the instrument's clinical implications; or (c) modify their clinical behavior in response to the instrument's results.
2	What was the impact on clinician behavior and patient-important outcomes?	No attempt was made to measure an impact of the score on physician's actions. However, the investigators hypothesize • "Most clinicians currently consider the creatinine clearance before PCI, but it is incumbent upon operators to recognize the additional risk factors for the development of RCIN after PCI, which collectively can have greater impact." (p. 1518) • "Evaluation of the amount of myocardial territory at stake should be weighed against the risk of RCIN given the associated increase in adverse events." (p. 1518) • "Choosing to use prophylactic measures in patients undergoing PCI with a RCIN risk score $\geq$ 5 would require tests on roughly 20% of all patients and target 90% of those at risk for PCIN." (p. 1518)

Limitations

1) **Use of LR rather than CART. Use of logistic regression rather than recursive partitioning. The former will build a model that simultaneously maximizes sensitivity and specificity. For ED risk stratification, we generally prefer to**

maximize sensitivity at the expense of specificity so recursive partitioning is often preferred.

2) **Reporting c-statistic rather than sensitivity and specificity.**

3) **No confidence intervals were reported.**

4) **Limited external validity (single-hospital, non-ED based sampling).**

5) **Failure to report full spectrum of hypothesized risk factors.**

6) **No chart review details on who collected outcomes data, when they collected it or whether these individuals were blinded to the study hypothesis.**

7) **No definitions for components of the risk score:**
   - **Urgent/emergency procedure**
   - **CHF**
   - **HTN**
   - **PVD**

   Without explicit definitions, one can expect variable interpretation of these parameters depending upon individual biases specific to their clinical environment.

Bottom Line

This CDR is of indeterminate significance based upon substantial methodological shortfalls, but individual risk factors are consistent with prior studies seeking to identify patients at high risk for CIN after PCA. The results demonstrate that CIN prolongs hospital LOS and is associated with adverse cardiac outcomes.