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Development of an easily applicable risk score model for contrast-induced nephropathy prediction after percutaneous coronary intervention
A novel approach tailored to current practice

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ABSTRACT

Background: Several risk factors for contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI) have been identified. The cumulative effect of these risk factors on renal function has been assessed with the development of risk score models in a number of studies. However, concerns were raised that estimates of the risk attributable to individual factors may be unreliable. We sought to develop a simple risk score for developing CIN after PCI irrespective of use of prophylactic measures and also capturing the effect of pre-intervention medication and presence of various co-morbidities.
Methods: Consecutive patients treated with elective or urgent PCI at our cardiac catheterization laboratory were enrolled (derivation cohort n = 488, validation cohort n = 200). CIN was defined as increase ≥25% and/or ≥0.5 mg/dl in serum creatinine at 48 h after PCI vs baseline. Multivariable logistic regression analysis was then performed to identify independent predictors of CIN (pre-existing renal disease, metformin use, history of previous PCI, peripheral arterial disease and ≥300 ml of contrast volume).
Results: The incidence of CIN in the development cohort was 10.2% with a significant trend across increasing score values ($p<0.001$). The model demonstrated good discriminating power (c-statistic 0.759) and excellent calibration (calibration slope 0.91). The model was validated internally by bootstrapping in 1000 samples (c-statistic 0.753) and in a cohort of 200 patients (c-statistic 0.864) demonstrating stable performance.
Conclusions: The proposed risk score is easily applicable and allows for practically simple risk assessment compared to other published scores while at the same time overcomes drawbacks of previous model designs.

1. Introduction

Radiologic procedures utilizing contrast media as a mean for organ or vessel imaging are now being widely applied for diagnostic and therapeutic purposes. This has led to an increasing incidence of procedure related contrast-induced nephropathy (CIN) [1]. CIN is responsible for approximately 10% of all iatrogenic renal insufficiency and is the third most common cause of hospital-acquired renal failure [2].

Although the risk of renal function impairment associated with radiologic procedures is low in the general population, it may be very high in selected patients' subsets, especially in cardiac procedures. Special conditions may contribute to renal injury in this setting such as predominant vascular atherosclerosis and reduced effective circulating arterial volume [3]. Indeed, contrast-medium induced nephropathy is a recognized complication in coronary diagnostic and interventional procedures [3]. Furthermore, its development has been associated with increased in-hospital and long-term morbidity and mortality, prolonged hospitalization and long-term renal impairment [1,4,5].

Given that the majority of patients currently undergoing invasive cardiovascular procedures are either outpatients or likely to be discharged within a short time-period (24–48 h) after the procedure, a practical means of predicting early renal function deterioration would be of clinical relevance. Many individual risk factors for the development of CIN have been reported in patients undergoing percutaneous coronary interventions (PCI) [1,4,6]. In addition, the cumulative effect of these risk factors on renal function has been assessed with the development of risk score models in a number of studies [7–9]. However, none of the databases accounted for co-morbidities, prophylactic interventions to prevent contrast nephropathy (i.e. administration of hydration or N-acetylcysteine) or

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the effect of pre-intervention treatment [10]. Furthermore, some risk scores were derived from patients undergoing primary PCI in the setting of acute myocardial infarction [9], and therefore may not apply in more general settings (such as elective PCI). Concerns were raised that estimates of the risk attributable to individual factors may be unreliable [3,10,11].

The aim of the present study was to develop a simple risk score that could be readily applied by clinicians to evaluate individual patient risk for developing CIN after PCI based on an unselected population of consecutive PCI patients, irrespective of use of prophylactic measures and also capturing the effect of pre-intervention medication and presence of various co-morbidities.

2. Material and methods

2.1. Study population

In the present study all consecutive patients who were treated with PCI on an elective or emergency basis at our cardiac catheterization laboratory between September 2008 and January 2010 were initially enrolled (n = 509). Patients on chronic peritoneal or hemodialytic treatment (n = 7) were excluded prior to entry into the study. Patients who died during hospitalization (n = 1), those having in-hospital coronary artery bypass grafting (CABG) (n = 2), and those treated with a repeated PCI (n = 11) within 1 week or less from the index procedure were also excluded from the analysis. The remaining 488 patients constituted the derivation cohort for risk score development.

A validation dataset comprising initially of 203 consecutive PCI patients was also enrolled from our center. Similarly to the derivation cohort, patients who where treated with a repeat PCI (n = 2) and patients with end-stage renal disease (n = 1) were not included. None of the patients in the validation cohort died during hospitalization or had an in-hospital CABG. Therefore the validation dataset comprised 200 patients.

The study was approved by the ethics committee of our institution and informed consent was obtained from all patients.

2.2. Study protocol

Patients underwent PCI according to current guidelines [12]. Routine hydration was performed with 1 ml/kg/h of normal (0.9%) saline for 18–24 h before PCI and 18 to 24 h post procedure. In patients with reduced left ventricular ejection fraction (<40%), presence of significant valvular disease or overt heart failure upon presentation, the hydration rate was reduced to 0.5 ml/kg/h. Special care was given regarding metformin use. According to current guidelines metformin was withheld for 48 h prior the procedure (for elective cases) and for 48 h post PCI (all cases) [11]. The use of N-acetylcysteine, platelet glycoprotein IIb/IIIa receptor inhibitors, and the indication to intra-aortic balloon pump (IABP) or intravenous inotropic support, was left to the discretion of the interventional cardiologists according to our institution clinical protocols.

Serum creatinine concentration for every patient was routinely measured at the time of admission (baseline — 18 to 24 h before PCI), at 24 h, 48 h and 7 days post procedure. Furthermore, for each patient procedural details (i.e., diseased coronary vessels, treated coronary vessels, contrast dose, procedure duration, number of stents employed) were recorded. A non-ionic, low-osmolarity contrast agent, ioversol (Optiray 350 mg iodine/ml, Mallinckrodt Medical Imaging, Ireland) was used for all procedures.

2.3. Definitions

"Contrast induced nephropathy" was defined as an increase of ≥25% or ≥0.5 mg/dl in pre-PCI serum creatinine at 48 h PCI [11]. Pre-existing renal disease was defined as previous admission for renal artery stenosis, acute renal failure, glomerulonephritis, obstruction, hematuria, nephrotic syndrome, or nephrectomy irrespective of baseline creatinine levels or glomerular filtration rate; peripheral arterial disease, as poorly palpable pulses, claudication, arterial bruits, previous vascular surgery, aortic aneurismal disease or verified atherosclerotic lesions causing stenosis ≥50% in major arteries (carotid, iliac, popliteal, femoral); anemia, as hematocrit value <39% for men and <36% for women; hypotension, as systolic blood pressure <90 mm Hg requiring inotropic support with medications or IABP; significant blood loss, as hemoglobin reduction below 8.0 g/dl, blood transfusion, or significant hematoma/arterial pseudoaneurysm requiring intervention.

Given the possible predictive impact of 'novel' contrast volume indexes in published literature [13,14], we also assessed for each patient contrast ratio and volume to creatinine clearance ratio. Contrast ratio was determined by dividing the administered contrast volume by the calculated maximum contrast dose [13] (maximum contrast dose (MCD) was calculated by using the formula proposed by Cigarroa and colleagues: MCD (ml) = 5 × body weight (kg)/serum creatinine (mg/dl) [15], with values >1 being significant predictors [13]). Volume to creatinine ratio was determined by dividing the volume of contrast received by the patient's creatinine clearance (with values >3.7 being significant predictors) [14]. The creatinine clearance was estimated using the Cockcroft–Gault method: 140-age (years) × weight (kg)/72 × serum creatinine (mg/dl) {× 0.85 for female subjects} [16]. Renal function was then categorized according to the stages set by the National Kidney Foundation with creatinine clearance ≥90 ml/min considered normal, 60–89 ml/min considered mildly impaired, and <60 ml/min considered at least moderately impaired [17].

2.4. Statistical analysis

Results for continuous variables are presented as means with standard deviation (SD) and as percentages for categorical data. Normality was tested using the Shapiro–Wilk test. The unpaired Student's t-test was used to evaluate unadjusted differences in continuous variables between the two groups. Comparisons between categorical variables were performed with the chi-square test or Fisher's exact test as appropriate.

Predictors of nephropathy after PCI were derived from >50 demographic, clinical, angiographic and procedural variables in the development dataset. The association between CIN and study variables was evaluated in univariable logistic regression analysis models. Multivariable logistic regression analysis was then performed to identify independent predictors of CIN. Study variables that were significant in the univariable analysis models were available for selection in the final model. For all logistic regression analysis models, odds ratios (OR) with 95% confidence intervals were calculated.

Model fit was assessed by the overall χ^2, the −2 Log likelihood (−2LL), and the goodness of fit Hosmer–Lemeshow statistic, while model predictive performance (discrimination) and calibration were assessed with the c-statistic and the calibration slope respectively [18,19].

The variables that were independently and significantly associated with CIN in the final multivariable model were assigned a weighted integer coefficient value based upon its beta value. Therefore, a risk score model was constructed where the final risk score for each patient represented the sum of integer coefficients.

A well-known problem of predictive multivariable models is that their performance is frequently overestimated because they are evaluated on the sample used for their construction. Such a phenomenon, known as 'optimism', is important for appropriate validation of multivariable models. We therefore, internally (within the derivation cohort) validated the performance of our model by bootstrapping [20]. Simulation studies have shown that this approach provides the least biased and most stable estimates of optimism-corrected performance among the various proposed methods for internal validation [21], with 'optimism' referring to the inherent bias toward an overestimated performance in the derivation dataset [20–22]. Briefly, optimism in a performance measure (e.g. the c-statistic) with this method is estimated by the average of the differences in the measure (measure in bootstrap sample − measure in original dataset) from a large number of models derived from respective bootstrap samples. This average of the measure (measure in bootstrap sample − measure in original dataset), i.e. the optimism, is then subtracted from the original performance measure (i.e. the c-statistic of the original model) to provide a more realistic estimate. This approach moderates our expectations from the model and sets an upper limit for performance in future external validation. We validated two measures of performance using 1000 bootstrap samples: the c-statistic; a measure of discrimination of the model and the slope of the linear predictor; a measure of model calibration. Furthermore, the model was also validated in a separate dataset (validation cohort). Power analysis suggested that a study sample of 200 patients with an estimated incidence of CIN approximately 10% renders the risk score model able to predict the development of CIN with a discriminating power (c-statistic) of at least 0.650 with a >90% power at a significance level of 0.05.

Finally, the prognostic significance of risk score on rates of major adverse cardiovascular events (MACE) occurring during 1-year follow up post-admission was also estimated in the derivation dataset. Death due to cardiac causes, hospitalization for re-infarction and repeat revascularization were considered as MACE.

A p value <0.05 was considered to indicate statistical significance; all tests were two-sided. The IBM PASW-SPSS Statistics 18.0 statistical software package (SPSS Inc, Chicago, Illinois, USA) was used for all calculations.

3. Results

3.1. Patients

CIN at 48 h post-procedure occurred in 10.2% of our derivation study population (50 of 488 patients). Baseline demographic, clinical and angiographic characteristics, as well as main procedural data are listed in Table 1. Overall the mean age was 64 years and there were 26% females. The mean baseline serum creatinine level was 1 mg/dl (SD 0.26 mg/dl) whereas 6% of study population had creatinine levels >1.5 mg/dl. 7% of patients had a history of chronic renal disease. Furthermore, the mean baseline estimated glomerular filtration rate (eGFR) was 86 ml/min/1.73 m^2 (SD 31 ml/min/1.73 m^2). Of interest, 18% of study population met the National Kidney Foundation cutoff for moderate impairment of eGFR (<60 ml/min/1.73 m^2).