Journal of the American Heart Association

ORIGINAL RESEARCH

A Biomarker-Enhanced Model for Prediction of Acute Kidney Injury and Cardiovascular Risk Following Angiographic Procedures: CASABLANCA AKI Prediction Substudy

Reza Mohebi, MD; Roland van Kimmenade, MD, PhD; Cian McCarthy, MB, BCh, BAO; Hanna Gaggin, MD, MPH; Roxana Mehran, MD; George Dangas, MD, PhD; James L. Januzzi, Jr, MD

BACKGROUND: The 2020 Acute Disease Quality Initiative Consensus provided recommendations on novel acute kidney injury biomarkers. In this study, we sought to assess the added value of novel kidney biomarkers to a clinical score in the CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) study.

METHODS AND RESULTS: We evaluated individuals undergoing coronary and/or peripheral angiography and added 4 candidate biomarkers for acute kidney injury (kidney injury molecule-1, interleukin-18, osteopontin, and cystatin C) to a previously described contrast-associated acute kidney injury (CA-AKI) risk score. Participants were categorized into integer score groups based on the risk assigned by the biomarker-enhanced CA-AKI model. Risk for incident cardiorenal outcomes during a median 3.7 years of follow-up was assessed. Of 1114 participants studied, 55 (4.94%) developed CA-AKI. In adjusted models, neither kidney injury molecule-1 nor interleukin-18 improved discrimination for CA-AKI; addition of osteopontin and cystatin C to the CA-AKI clinical model significantly increased the c-statistic from 0.69 to 0.73 (*P* for change <0.001) and resulted in a Net Reclassification Index of 59.4. Considering those with the lowest CA-AKI integer score as a reference, the intermediate, high-risk, and very-high-risk groups were associated with adverse cardiorenal outcomes. The corresponding hazard ratios of the very-high-risk group were 3.39 (95% CI, 2.14–5.38) for nonprocedural acute kidney injury, 5.58 (95% CI, 3.23–9.63) for incident chronic kidney disease, 6.21 (95% CI, 3.67–10.47) for myocardial infarction, and 8.94 (95% CI, 4.83–16.53) for all-cause mortality.

CONCLUSIONS: A biomarker-enhanced risk model significantly improves the prediction of CA-AKI beyond clinical variables alone and may stratify the risk of future cardiorenal outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00842868.

Key Words: chronic kidney disease ■ contrast-associated acute kidney injury ■ coronary angiography ■ coronary artery disease ■ mortality

People who undergo coronary and peripheral angiography are at risk of contrast-associated acute kidney injury (CA-AKI),[1] a common and potentially serious angiography complication whose underlying mechanism is not fully understood.[2] Once CA-AKI occurs, treatment options are limited; accordingly, prevention therapy is the main approach to address CA-AKI, minimizing the volume of contrast media and intravenous hydration before and after the procedure, which may not be appropriate for all patients, such as those with heart failure.[3] Notably, cardiac risk has been associated with CA-AKI, with studies linking CA-AKI with a higher mortality rate and adverse future cardiovascular events,[4] and risk for

Correspondence to: James L. Januzzi Jr, MD, FACC, Massachusetts General Hospital, Cardiology Division, 55 Fruit Street Boston, MA 02114.
Email: jjanuzzi@partners.org

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.025729

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- A recent consensus recommended exploration of biomarkers for prediction of contrast-associated acute kidney injury (CA-AKI).
- Among a cohort of people undergoing coronary angiography, we validated a recently described clinical risk score for CA-AKI and explored how biomarkers might improve its performance.
- Incorporation of osteopontin and cystatin C to the clinical risk model improved accuracy for predicting CA-AKI and also predicted major adverse cardiovascular and renal events during follow-up.

What Are the Clinical Implications?

- The biomarker-enhanced CA-AKI model can help health care professionals to identify patients at risk of CA-AKI before angiographic procedures.
- The biomarker-enhanced CA-AKI model provides important information regarding risk of future cardiorenal events in patients undergoing angiographic procedures.

Nonstandard Abbreviations and Acronyms

CA-AKI	contrast-associated acute kidney injury
CASABLANCA	Catheter Sampled Blood Archive in Cardiovascular Diseases Study
KIM-1	kidney injury molecule-1

future CA-AKI events follows patients that may require iterative contrast-enhanced procedures; furthermore, future progression of chronic kidney disease (CKD) may also be more likely in those with incident CA-AKI. Given limited treatment options once CA-AKI develops and an unfavorable associated prognosis, early identification of those at risk of CA-AKI is crucial. In addition, with improvement of non–iodine contrast ischemia detection, it is important to expose subjects to angiography only when there is a high a priori chance of interventional options.

As AKI is a heterogeneous clinical syndrome with a broad range of etiologies, its prediction may be challenging. To facilitate identifying those at higher risk for CA-AKI, clinical risk models have been developed; recently, Mehran and colleagues described an updated clinically based CA-AKI risk score predicting both CA-AKI and cardiovascular events after angiographic procedures.[5] Such clinical models have clear advantages; however, given the complexity of the biological processes leading to CA-AKI, studies have also investigated the role of different biomarkers in prediction or early diagnosis of AKI, including a focus on kidney function markers (such as cystatin C) and biomarkers associated with kidney injury.[6]

Given the proliferation of AKI biomarker studies, in 2020, a consensus statement was released regarding how best to incorporate kidney biomarkers into clinical practice.[7] The statement identified 20 promising biomarkers of kidney injury and recommended that a combination of damage and functional biomarkers along with clinical information be considered for improving the predictive accuracy for AKI in clinical practice.

To the extent the CA-AKI risk model described by Mehran and colleagues lacked biomarkers recommended by the recent consensus statement, we sought to evaluate the addition of candidate biomarkers to the model, including interleukin 18, kidney injury molecule-1 (KIM-1), osteopontin, and cystatin C to improve risk prediction of acute CA-AKI following the procedure among patients who undergo coronary and peripheral angiography. We further examined whether a biomarker-leveraged CA-AKI score can predict long-term clinical outcomes.

METHODS

All study procedures were approved by the Massachusetts General/Brigham Institutional Review Board, and informed consent was obtained from study participants. The data underlying this article cannot be shared publicly because of proprietary restrictions.

Study Design and Participants

The design of the CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases ; NCT00842868) study has been described previously.[8] Briefly, 1251 patients undergoing coronary or peripheral angiography with or without intervention between 2008 and 2011 were prospectively enrolled at the Massachusetts General Hospital in Boston, Massachusetts, with a goal to evaluate the role of clinical and biomarker information to predict periprocedural complications, including AKI. Patients were referred for angiography for various acute and nonacute indications, including acute coronary syndromes, heart failure, abnormal stress tests, stable chest pain, claudication, and routine preoperative evaluation. After excluding patients with missing values on serum creatinine after the index angiography (n=137), our final study cohort for this analysis consisted of 1114 patients (Figure S1).

Follow-Up

Medical record review from the time of enrollment to the end of follow-up was performed. Median follow-up was 3.7 years with a maximum follow-up of 8 years. To identify clinical end points, reviews of medical records and phone follow-up with patients and/or managing physicians were performed. The Social Security Death Index and/or postings of death announcements were used to confirm vital status. A detailed definition of end points for CASABLANCA was previously published.[8] Specific to this analysis, end point adjudication was performed using the guidance of the Universal Definition of Myocardial Infarction.[9]

Definitions for Kidney Outcomes

All kidney outcomes were adjudicated as described.[8] Results of serum creatinine as measured via the standard of care were used for the ascertainment of AKI, with CA-AKI defined as an absolute increase of ≥0.3 mg/dL and/or ≥50% relative increase in serum creatinine after angiography compared with the preprocedure serum creatinine level occurring up to 7 days after the intravascular administration of contrast medium when no alternative etiology for AKI was identified.[10] Progression to CKD was defined as progression from baseline estimated glomerular filtration rate (eGFR) ≥60 mL/min per 1.73 m^2 to an eGFR <60 mL/min per 1.73 m^2 at study conclusion. We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate eGFR.

Biomarker Testing

A total of 15 mL of blood was obtained immediately before and after the angiographic procedure through a centrally placed vascular access sheath. The blood was immediately centrifuged for 15 minutes and serum and plasma aliquoted on ice and frozen at −80 °C until biomarker measurement. The samples for this study were analyzed after the first freeze-thaw cycle for baseline biomarker values only. Specific to this study, we measured concentrations of interleukin-18 (Myriad RBM, Austin, TX), KIM-1 (Singulex Inc, Alameda, CA), cystatin C (Siemens, Inc, Newark, DE), and osteopontin (Myriad RBM).

Statistical Analysis

Median (interquartile) and count (frequency) were used to demonstrate the baseline characteristic of the study population. Distributions of baseline characteristics were compared between those who developed CA-AKI and those free of CA-AKI using Student's *t* test and the chi-squared test for continuous and categorical variables, respectively. Overall, 6.7% of data were missing. We used the Multivariable Imputation via Chained Equations package in R (R Foundation for Statistical Computing, Vienna, Austria) for data imputation. Since no standard exists regarding optimized cut points for each biomarker for prediction of CA-AKI, we used the "cutpointr" package (method: "maximize_metric", metrics: "sum_sens_spec") to calculate the optimized biomarker cut point for detection of CA-AKI based on the highest sensitivity and specificity. Accordingly, for each biomarker, the elevated value was defined as ≥219 pg/mL for interleukin-18, ≥236 pg/mL for KIM-1, ≥32 pg/mL for osteopontin, and ≥0.92 mg/L for cystatin C. Logistic regression analysis was implemented to assess the factors associated with CA-AKI. Three markers of kidney injury (interleukin-18, KIM-1, osteopontin) plus one biomarker of kidney function (cystatin C) were entered into in the univariate logistic regression model. Those with a *P* value <0.2 were retained and combined with the clinical CA-AKI risk score[5] (age; eGFR; heart failure; diabetes; clinical presentation: asymptomatic/stable, unstable; acute myocardial infarction; hemoglobin; left ventricular ejection fraction; and blood glucose). To assess the added value of kidney biomarkers to the score, change in discrimination was evaluated with Harrell's c statistic. Moreover, the Integrated Discrimination Index and Net Reclassification Index were calculated to assess reclassification.

Once a final biomarker-enhanced model for CA-AKI was developed, to translate the information into a clinically actionable tool, an integeric risk score was developed. To do so, the integeric score from the original CA-AKI model[5] was preserved, and the biomarker log-odds coefficients from the logistic model were used to generate integers to incorporate into the biomarker-enhanced CA-AKI model. This led to a score with a maximum value of 28; however, no study participant had all risk factors in our study, so the maximum value was 22.

Once biomarkers were fitted into the risk model, study participants were categorized into risk quartiles: 1 to 5 points (low risk), 6 to 11 points (intermediate risk), 12 to 16 (high risk), and 17 to 22 (very high risk). The frequency of CA-AKI was then assessed across these score groupings.

Cox proportional hazard regression analysis was then used to assess the association of integeric risk category and cardiorenal outcomes during an average of 3.7 years, including nonprocedural AKI, heart failure, myocardial infarction, cardiovascular death, and all-cause mortality. The proportional hazard assumption in the Cox model was assessed with the Schoenfeld residual test, and all proportionality assumptions were appropriate. All *P* values reported were 2-sided. A *P* value <0.05 was considered statistically significant. All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing; https://www.R-project.org/).

RESULTS

Among study participants, the median concentration (quartile 1–quartile 3) was 200.5 (148.0–269.0) for interleukin-18, 152.3 (99.8–254.0) for KIM-1, 28 (21–43) for osteopontin, and 0.81 (0.70–1.02) for cystatin C. Of 1114 individuals who underwent angiography, 55 (4.94%) were adjudicated as developing CA-AKI. Patients who developed CA-AKI were older; were more likely to have prevalent diabetes and CKD; and had higher blood urea nitrogen, KIM-1, osteopontin, and cystatin C concentrations. Data are presented in Table 1.

Table 2 demonstrates the associations of kidney biomarkers with incident CA-AKI. In the univariate model, elevated interleukin-18 concentration (odds ratio [OR], 0.64; 95% CI, 0.30–1.23; P=0.21) was not significantly associated with CA-AKI. In contrast, elevated concentrations of KIM-1 (OR, 2.24; 95% CI, 1.29–3.87; P=0.004), osteopontin (OR, 3.65; 95% CI, 2.05–6.80; P<0.001) and cystatin C (OR, 3.13; 95% CI, 1.81–5.55; P<0.001) were associated with CA-AKI. In a multivariable model adjusted for clinical CA-AKI components, the OR of CA-AKI was 1.26 (95% CI, 0.69–2.28; P=0.46) for elevated KIM-1, 2.39 (95% CI, 1.25–4.73; P=0.01) for elevated osteopontin, and 2.29 (95% CI, 1.20–4.467; P=0.01) for elevated cystatin C. Although elevated concentrations of KIM-1, osteopontin, and cystatin C following the procedure were associated with subsequent CA-AKI, the amount of change in concentration of biomarkers from before to after the procedure did not add to the ability of the baseline value to CA-AKI (all P>0.05).

Table 3 shows the performance of the logistic model–based CA-AKI risk score and added value of biomarkers. The clinical CA-AKI risk model had a c-statistic of 0.69. Addition of osteopontin and cystatin C concentrations to the clinical CA-AKI risk model yielded an increase in c-statistic from 0.69 to 0.73. Moreover, it resulted in a significant reclassification improvement from the clinical CA-AKI risk score as evidenced by a continuous Net Reclassification Index of 59.4 (95% CI, 33.35–84.93; P<0.001), and Integrated Discrimination Index of 1.7 (95% CI, 0.8–2.6; P<0.001).

To allow for clinical interpretation, CA-AKI integer scores were calculated for study participants on the basis of the models described above (detailed in Table 2); the overall CA-AKI integeric risk score is shown in Table S1. Distributions of integeric CA-AKI scores are shown in Figure S2, which reveals a non-normal distribution, with a positive skew: The majority of study participants had scores clustered in the lower range, with a mode value of 4 and median value of 6 (25th–75th percentile, 4–10). Participants were categorized by CA-AKI integer score into quartiles: low-risk score, 1 to 5; intermediate-risk score, 6 to 11; high-risk score, 12 to 16; and very-high-risk score,17 to 22. In doing so, there was an increase in CA-AKI occurrence across these risk groups (Figure 1). As shown in the figure, those in the highest quartile had the most significant risk of CA-AKI.

During a median of 3.7 years (maximum 8 years) of follow-up, there were 335 cases of nonprocedural AKI, 261 cases of progressions to CKD, 302 heart failure events, 202 myocardial infarction events, 143 cardiovascular deaths, and 188 all-cause deaths. Hazard ratios (HRs) of CA-AKI integer score groups for predicting adverse cardiorenal outcomes are shown in Table 4. This demonstrates that when compared with participants in the low-risk (score 1–5) category, those in intermediate-risk (score 6–11), high-risk (score 12–16) or very-high-risk (score 17–22) score categories had a substantially higher risk for each outcome examined, with very-high-risk individuals demonstrating the most elevated HR. For example, very-high-risk study participants had the greatest likelihood for incident nonprocedural AKI (HR, 3.39; P<0.001), CKD progression (HR, 5.58; P<0.001), heart failure (HR, 4.09; P<0.001), acute myocardial infarction (HR, 6.21; P<0.001), cardiovascular death (HR, 10.51; P<0.001), and all-cause death (HR, 8.94; P<0.001). Cumulative incidence rates based on the Cox model of risk categories for cardiorenal outcomes using integeric score groupings are shown in Figure 2.

DISCUSSION

Among 1114 individuals undergoing coronary and/or peripheral angiography in the CASABLANCA study, we observed that ≈1 of 20 patients developed CA-AKI. The present analysis provides external validation of a previously described clinical CA-AKI risk score but extends the understanding of this risk model by enhancing accuracy through the addition of kidney biomarkers: Through the addition osteopontin and cystatin C, the preexisting score[5] was extended; in doing so, study participants could be grouped into a range of risk categories, with accuracy for CA-AKI prediction and discrimination for subsequent cardiorenal outcomes. These results follow guidance from the 2020 Acute Disease Quality Initiative Consensus statement[7] by adding biomarkers to clinical models to enhance clinical risk prediction for CA-AKI.

Depending on the definition used for CA-AKI and patient characteristics, CA-AKI occurs at varying rates ranging from 4% to 15%[11]; our results are consistent with this general incidence. Early identification of individuals with impending CA-AKI is still an unmet need with efforts including clinical models

Table 1. Demographic, Clinical, and Laboratory Characteristics of Study Participants

	No CA-AKI (N=1059)	CA-AKI (N=55)	*P* value
Age, mean (SD)	66.5 (11.4)	70.5 (11.4)	0.01
Sex, male, n (%)	766 (72.33)	36 (65.45)	0.27
Race, White, (n) %	986 (93.1)	54 (98.2)	0.58
Clinical variables, n (%)			
Hypertension	807 (76.2)	47 (85.45)	0.11
Diabetes	265 (25.02)	22 (40)	0.01
Heart failure	221 (20.87)	15 (27.27)	0.26
CAD	548 (51.75)	33 (60)	0.23
CKD	141 (13.31)	12 (21.82)	0.07
Smoking %	146 (13.79)	5 (9.09)	0.32
Atrial fibrillation/flutter	213 (20.11)	11 (20)	0.98
CVA/TIA	119 (11.24)	7 (12.73)	0.73
Prior angioplasty	290 (27.38)	19 (34.55)	0.25
Prior stent	656 (61.95)	38 (69.09)	0.29
Prior CABG	190 (17.94)	12 (21.82)	0.47
Medications, n (%)			
ACE inhibitors	433 (40.89)	26 (47.27)	0.35
ARB	162 (15.3)	19 (34.55)	<0.001
Beta blocker	757 (71.48)	37 (67.27)	0.50
MRA	45 (4.25)	2 (3.64)	0.83
Loop diuretics	223 (21.06)	20 (36.36)	0.007
Nitrates	202 (19.07)	17 (30.91)	0.03
CCB	272 (25.68)	17 (30.91)	0.39
Statin	814 (76.86)	41 (74.55)	0.69
Aspirin	782 (73.84)	37 (67.27)	0.28
Clopidogrel	245 (23.14)	13 (23.64)	0.93
Warfarin	170 (16.05)	11 (20.00)	0.44
Laboratory variables, median (quartile 1–quartile 3)			
Sodium	140 (138–141)	140 (137–140.5)	0.27
Blood urea nitrogen	18 (15–24)	22 (16.5–30)	0.03
Blood glucose	102 (91–119)	103 (91–137.5)	0.35
Creatinine	1.06 (0.9–1.3)	1.13 (0.91–1.45)	0.70
eGFR	65.08 (51.52–79.14)	54.37 (42.25–78.13)	0.29
Interleukin-18 before procedure	201 (148–270.5)	195 (140–257.5)	0.95
Interleukin-18 after procedure	186 (134–247.5)	164 (128.5–221.5)	0.77
Osteopontin before procedure	28 (20–42)	43 (28.5–66)	0.009
Osteopontin after procedure	28 (20–42)	42 (27–60.5)	0.03
KIM-1 before procedure	150.27 (99.1–247.87)	181.62 (117.77–389.77)	0.04
KIM-1 after procedure	137.22 (91.85–233.01)	175.18 (111.48–360.13)	0.04
Cystatin C before procedure	0.80 (0.70–1.01)	0.99 (0.76–1.39)	0.04
Cystatin C after procedure	0.76 (0.66–0.96)	0.88 (0.71–1.20)	0.16

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CA-AKI, contrast-associated acute kidney injury; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule-1; MRA, mineralocorticoid receptor antagonist; and SD, standard deviation.

for its prediction.[12–14] Mehran and colleagues[5] described a clinical CA-AKI risk score, which includes key clinical and laboratory factors, such as clinical presentation; clinical history of diabetes, anemia, or heart failure; age; blood glucose; and eGFR. In its derivation, this clinical model had a c-statistic of 0.72 for the prediction of incident CA-AKI; we have validated this performance with a similar C-statistic in

Table 2. Association of Kidney Biomarkers With CA-AKI in a Logistic Model

	Univariate model		Multivariable biomarker model		Clinical CA-AKI risk score* +biomarkers		Integer score
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	
Elevated interleukin-18	0.64 (0.30–1.23)	0.21	…		…		…
Elevated KIM-1	2.24 (1.29–3.87)	0.004	1.26 (0.69–2.28)	0.46	…		…
Elevated osteopontin	3.65 (2.05–6.80)	<0.001	2.39 (1.25–4.73)	0.01	2.11 (1.08–4.29)	0.02	4
Elevated cystatin-C	3.13 (1.81–5.55)	<0.001	2.29 (1.20–4.47)	0.01	2.43 (1.18–4.99)	0.03	4

Based on coefficients from the model, an integeric score was assigned to the significant biomarker acute kidney injury predictors. Elevated concentration was defined as ≥219 pg/mL for interleukin-18, ≥236 pg/mL for KIM-1, ≥32 pg/mL for osteopontin, and ≥0.92 mg/L for cystatin C. CA-AKI indicates contrast-associated-acute kidney injury; and KIM-1, kidney injury molecule-1.

*Clinical CA-AKI risk score: age, estimated glomerular filtration rate, blood glucose, heart failure, diabetes, presentation: asymptomatic/stable, unstable, acute myocaedial infarction, hemoglobin, left ventricular ejection fraction.

CASABLANCA (C-statistic=0.69). Given the biological complexity of CA-AKI, the addition of biological measures to clinical models such as the Mehran CA-AKI score was a testable hypothesis and consistent with recommendations from the 2020 Acute Disease Quality Initiative Consensus statement,[7] which recommended exploration of biomarkers to enhance prediction of CA-AKI. However, despite the enthusiasm to approach the problem of CA-AKI with a clinical and biomarker-enhanced approach, a substantial lack of data exists regarding whether biomarkers add to clinical variables to improve discrimination, calibration, and reclassification of risk models. Since the CASABLANCA study population is representative of a higher-risk group of typical individuals undergoing coronary angiography, we made use of the resources of the study biorepository to study several potential candidates. In this analysis, we also demonstrate the ability of the biomarker-leveraged CA-AKI score to predict future cardiorenal outcomes. Although the original CA-AKI tool was not developed for predicting such outcomes, given the strong link between risk for (and development of) CA-AKI and hard cardiorenal outcomes,[5] the fact that the biomarker-leveraged CA-AKI score is able to predict such events is both novel and reassuring.

Table 3. Reclassification Improvement of a Logistic Model From Adding Biomarkers to Clinical Risk Factors for Predicting CA-AKI

	Clinical CA-AKI risk score alone	Clinical CA-AKI+biomarkers
Harrell's c statistics	0.69	0.73
Brier score	0.046	0.044
IDI	…	1.7 (0.8–2.6)**
NRI continuous	…	59.4 (33.35–84.93)**

Clinical CA-AKI model: age; estimated glomerular filtration rate; blood glucose; heart failure; diabetes; presentation: asymptomatic/stable, unstable; acute myocardial infarction; hemoglobin; left ventricular ejection fraction. Clinical CA-AKI+biomarkers: clinical CA-AKI model+elevated concentration of osteopontin, cystatin C. CA-AKI indicates contrast-associated acute kidney injury; IDI, Integrated Discrimination Index; and NRI, Net Reclassification Index.

***P*-value <0.001.

Osteopontin is an extracellular structural protein synthesized by various cell types, including osteoblasts, smooth muscle, cardiac fibroblasts, endothelial cells, and macrophages.[15] Histologically, osteopontin is found in the loop of Henle and distal nephrons in normal kidneys. Recent studies have found that osteopontin has a critical role in tubulogenesis, cell apoptosis, promotion of cell regeneration, nitric oxide synthesis, and calcium oxalate crystal inhibition in the kidney.[16–18] Few studies have investigated the role of osteopontin in the detection of AKI. Lorenzen and colleagues[19] found that critically ill patients with AKI have higher osteopontin concentrations than critically ill patients without AKI. In the present study, osteopontin concentrations predicted CA-AKI independent of other biomarkers or clinical variables, and enhanced cardiorenal risk stratification extending its potential as a candidate biomarker for AKI risk assessment.

Unlike the proposed role of osteopontin as a kidney injury marker, cystatin C is a sensitive kidney function biomarker. It is an extracellular protease inhibitor found virtually in all tissues and body fluids with low molecular weight; 99% of circulating cystatin C is filtered in the renal glomeruli and reabsorbed totally in the proximal tubule without secretion, making it an ideal marker for estimating glomerular filtration rate.[20] Our findings corroborate recent studies supporting the use of cystatin C for predicting cardiorenal complications after angiography[21,22] and show how a biomarker linked to kidney function may be linked together with a kidney injury

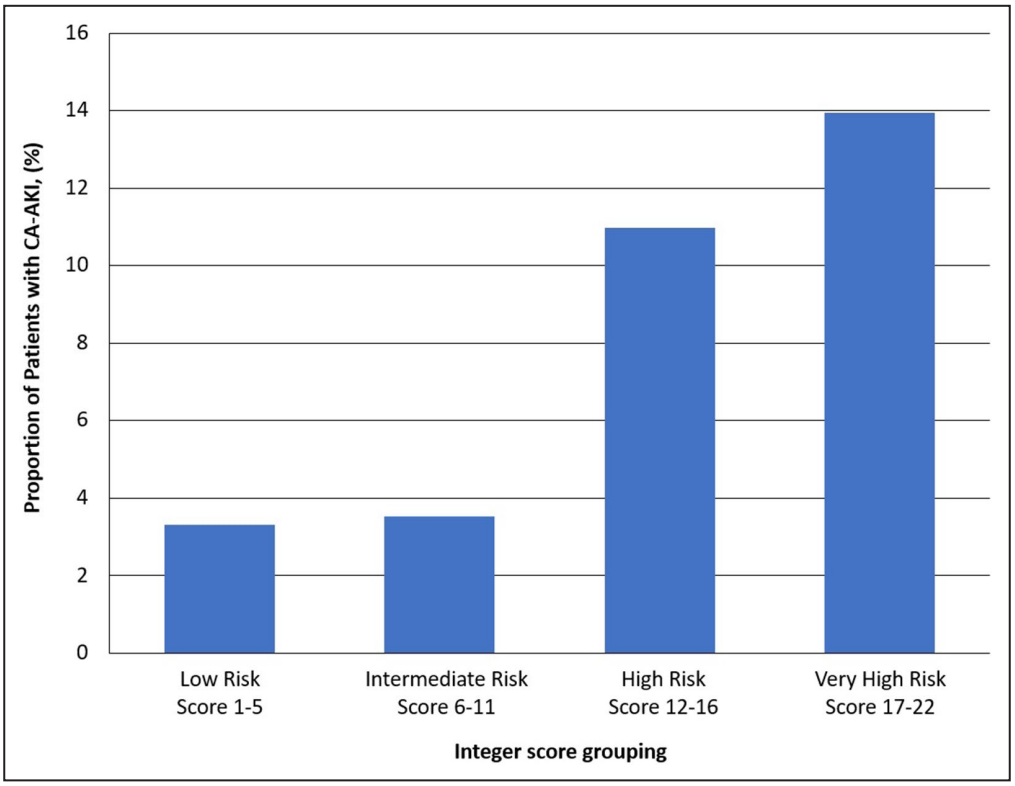


Figure 1. Study participants grouped by integeric risk score quartile.
Higher scores were associated with increased risk for contrast-associated acute kidney injury. CA-AKI indicates contrast-associated acute kidney injury.

marker to better discriminate risk for AKI and cardiac events.

We were not able to show that either KIM-1 or interleukin-18 were predictive of CA-AKI in fully adjusted models. KIM-1 is a transmembrane glycoprotein minimally expressed in normal adult kidneys. KIM-1 upregulation has been observed in proximal tubule epithelial cells following acute tubular necrosis.[23,24] Previously, we showed that elevated blood concentration of KIM-1 was associated with an increased risk of CA-AKI and CKD progression among CASABLANCA participants[6] but did not consider its role relative to established clinical models or other AKI biomarkers. Although KIM-1 appears generally promising for CA-AKI prediction,[25] once osteopontin was included in the model, the association of KIM-1 with CA-AKI was attenuated. Regarding interleukin-18, urine interleukin-18 concentrations were linked to AKI in a previous study,[26] but the role of blood interleukin-18 measurement in predicting CA-AKI remained less established. To our knowledge, this is the first examination of blood interleukin-18 with CA-AKI risk; our results indicated no specific relationship between the biomarker concentration and CA-AKI risk. Hence, we did not include interleukin-18 in our final clinical+biomarker model.

Although both pre- and postprocedure concentrations of biomarkers were associated with CA-AKI, the degree of biomarker change from before to after the procedure was not associated with an enhanced ability to predict CA-AKI, nor was the volume of contrast used. This implies that biological processes rendering risk for CA-AKI (including active kidney injury) may be active even before contrast administration and risk for substantial worsened kidney function precipitated by a second hit—in this case, angiography. Clinically, a sample could theoretically be obtained before an angiographic procedure and combined with clinical variables to be aware of CA-AKI risk. Doing so might provide an opportunity to provide prophylactic hydration, stage angiography to reduce intraprocedural dye administration, and even allow a window period for interventions to reduce CA-AKI after the procedure.

Our study has several limitations. First, in this analysis, we measured both KIM-1 and interleukin-18 in blood, rather than in urine. This may reduce the predictive value of both markers for AKI. On the other hand, in an animal study, Sabbisetti et al[24] showed that blood KIM-1 concentrations significantly increased following ischemia- or toxin-induced kidney injury, and both directly reflect the degree of functional and

Table 4. Hazard Ratio (95% CI) of CA-AKI+Biomarker Risk Score Group to Predict Future Cardiorenal Outcomes

	Low risk	Intermediate risk	High risk	Very high risk
	Score 1–5	Score 6–11	Score 12–16	Score 17–22
Nonprocedural AKI				
Event rate, n (%)	86 (18.9)	159 (35.1)	67 (43.2)	23 (44.2)
HR (95% CI)	1	2.16 (1.67–2.81)	3.13 (2.27–4.31)	3.39 (2.14–5.38)
P value	…	<0.001	<0.001	<0.001
Progression of CKD				
Event rate, n (%)	72 (17.1)	124 (136.0)	49 (45.0)	16 (53.3)
HR (95% CI)	1	2.71 (2.03–3.63)	4.36 (3.02–6.28)	5.58 (3.23–9.63)
P value	…	<0.001	<0.001	<0.001
Heart failure				
Event rate, n (%)	75 (16.5)	144 (31.8)	58 (37.4)	25 (48.1)
HR (95% CI)	1	2.16 (1.63–2.85)	2.76 (1.96–3.89)	4.09 (2.60–6.44)
P value	…	<0.001	<0.001	<0.001
Myocardial infarction				
Event rate, n (%)	41 (9.0)	99 (21.9)	41 (26.5)	21 (40.4)
HR (95% CI)	1	2.77 (1.92–3.98)	3.98 (2.57–6.16)	6.21 (3.67–10.47)
P value	…	<0.001	<0.001	<0.001
Cardiovascular death				
Event rate, n (%)	15 (3.3)	67 (14.8)	48 (31.1)	13 (25.0)
HR (95% CI)	1	5.09 (2.95–8.08)	13.30 (7.59–23.30)	10.51 (5.06–21.83)
P value	…	<0.001	<0.001	<0.001
Total death				
Event rate, n (%)	24 (5.3)	89 (19.6)	57 (36.8)	18 (34.6)
HR (95% CI)	1	4.21 (2.68–6.62)	9.74 (6.02–15.76)	8.94 (4.83–16.53)
P value	…	<0.001	<0.001	<0.001

When converted to an integeric risk score, the CA-AKI+biomarker model had good discrimination for predicting incident cardiorenal outcomes. AKI indicates acute kidney injury; CKD, chronic kidney disease; and HR, hazard ratio.

histologic kidney injury, while in work from our own group (using the same KIM-1 measurements) we previously reported plasma KIM-1 associated with AKI in a lesser-adjusted model. To our knowledge, this is the first examination of blood interleukin-18 with CA-AKI risk; while consensus recommendations suggest exploration of this biomarker in urine, it is plausible that blood values might reflect risk for AKI. It may be, like KIM-1, that interleukin-18 measurement might be more predictive if measured in urine, essentially closer to the target organ damage. A second limitation is that >90% of CASABLANCA participants were White individuals. Hence, we could not assess the disparities in kidney outcome across different races or ethnicities, which may limit our model's generalizability. Although these data are, in a sense, external validation of the original clinical CA-AKI score, a third limitation is the lack of internal or external validation of the biomarker-leveraged score. The lack of available validation cohorts illustrates the importance of our work and need for further research into the value of biomarkers to support assessment of CA-AKI. Fourth, other blood kidney injury biomarkers (retinol-binding protein, tumor necrosis factor, neutrophil gelatinase–associated lipocalin, hepcidin, liver-type fatty acid–binding protein, proenkephalin A) were not available in CASABLANCA. Fifth, we used 3 different performance measures to quantify the added value of biomarkers; although there is no ideal method,[27] the Net Reclassification Index value and the improvement in prediction ability of the model with addition of biomarkers may be interpreted with caution given the proposed limitations of Net Reclassification Index.[28] Finally, while CASABLANCA was originally designed and powered to evaluate for risk of CA-AKI, we did not correct for multiple comparisons in our statistical methods.

In conclusion, CA-AKI frequently occurs in people who undergo coronary and peripheral angiography. A biomarker-enhanced CA-AKI prediction model may help early detection of impending CA-AKI and further risk-stratify patients undergoing coronary/peripheral angiography for adverse cardiovascular outcomes.

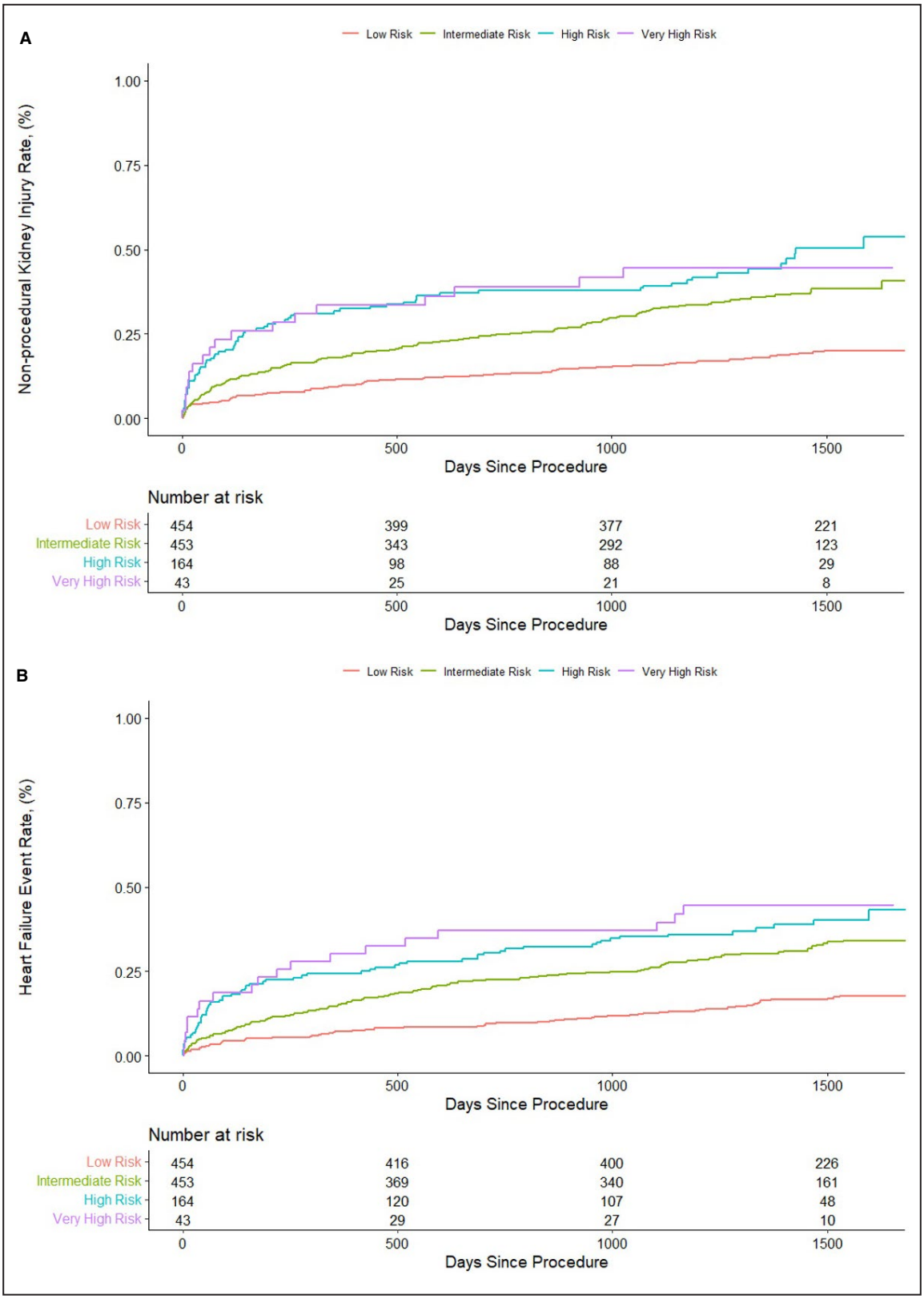


Figure 2. The cumulative incidence rate of (A) nonprocedural acute kidney injury, (B) heart failure event, (C) myocardial infarction/cardiovascular death, and (D) all-cause death by integeric risk category.
Categories were low risk (1–5 points), intermediate-risk (6–11 points), high risk (12–16 points), and very high risk (17–22 points).

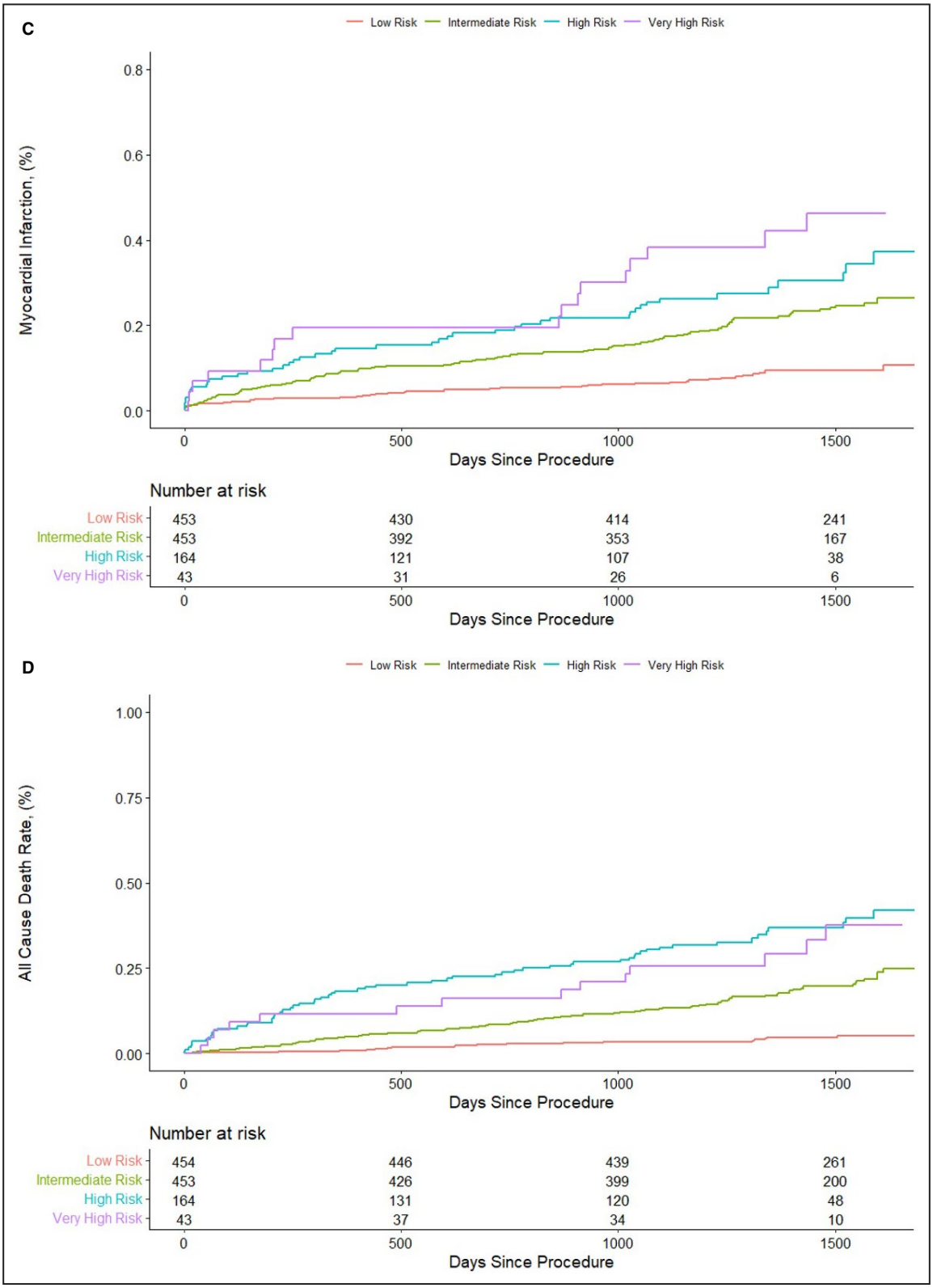


Figure 2. **(Continued)**

ARTICLE INFORMATION

Received February 22, 2022; accepted March 17, 2022.

Affiliations

Massachusetts General Hospital, Boston, MA (R. Mohebi., C.M., H.G., J.L.J.); Harvard Medical School, Boston, MA (R. Mohebi., C.M., H.G., J.L.J.); Cardiology Division, Radboud UMC, Nijmegen, the Netherlands (R.v.K.); The Zena and Michael A Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY (R. Mehran., G.D.); and Baim Institute for Clinical Research, Boston, MA (J.L.J.).

Acknowledgments

The authors thank Prof. Stuart Pocock for his insightful statistical advice.

Sources of Funding

Dr Mohebi is supported by the Barry Fellowship. Dr McCarthy is supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant (5T32HL094301-12). Dr Januzzi is supported by the Hutter Family Professorship.

Disclosures

Dr van Kimmenade has received research grants from Novartis. Dr Gaggin has received research grants support from Roche Diagnostics, Jana Care, Ortho Clinical, Novartis, Pfizer, Alnylam, and Akcea; consulting income from Amgen, Eko, Merck, Roche Diagnostics, and Pfizer; stock ownership for Eko; and research payments for clinical end point committees from Radiometer. She has also received research payment for clinical end point committees from Baim Institute for Clinical Research for Abbott, Siemens, and Beckman Coulter. Dr Mehran reports institutional grants from Abbott Laboratories, AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers Squibb, Chiesi, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, and OrbusNeich; personal fees from Boston Scientific, Janssen, Scientific Affairs, Sanofi, and Siemens Medical Solutions; consultant fees paid to the institution from Abbott Laboratories and Bristol Myers Squibb; and advisory board funding paid to the institution from Spectranetics/Philips/Volcano Corp. Dr Januzzi is supported by the Hutter Family Professorship; is a trustee of the American College of Cardiology; is a board member of Imbria Pharmaceuticals; has received grant support from Abbott Diagnostics, Applied Therapeutics, Innolife, and Novartis; has received consulting income from Abbott Diagnostics, Boehringer-Ingelheim, Janssen, Novartis, and Roche Diagnostics; and participates in clinical end point committees/data safety monitoring boards for AbbVie, Siemens, Takeda, and Vifor. The remaining authors have no disclosures to report.

Supplemental Material

Table S1
Figures S1–S2

REFERENCES

1. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004;44:1393–1399. doi: 10.1016/j.jacc.2004.06.068
2. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264. doi: 10.1161/01.CIR.0000016043.87291.33
3. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol*. 2008;51:1419–1428. doi: 10.1016/j.jacc.2007.12.035
4. Pucelikova T, Dangas G, Mehran R. Contrast-induced nephropathy. *Catheter Cardiovasc Interv*. 2008;71:62–72. doi: 10.1002/ccd.21207
5. Mehran R, Owen R, Chiarito M, Baber U, Sartori S, Cao D, Nicolas J, Pivato CA, Nardin M, Krishnan P, et al. A contemporary simple risk score for prediction of contrast-associated acute kidney injury after percutaneous coronary intervention: derivation and validation from an observational registry. *Lancet*. 2021;398:1974–1983. doi: 10.1016/S0140-6736(21)02326-6
6. Ibrahim NE, McCarthy CP, Shrestha S, Lyass A, Li Y, Gaggin HK, Simon ML, Massaro JM, D'Agostino RB, Garasic JM, et al. Blood kidney injury molecule-1 predicts short and longer term kidney outcomes in patients undergoing diagnostic coronary and/or peripheral angiography-Results from the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) study. *Am Heart J*. 2019;209:36–46. doi: 10.1016/j.ahj.2018.12.001
7. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, Bell M, Forni L, Guzzi L, Joannidis M, et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. *JAMA Netw Open*. 2020;3:e2019209. doi: 10.1001/jamanetworkopen.2020.19209
8. Gaggin HK, Liu Y, Lyass A, van Kimmenade RRJ, Motiwala SR, Kelly NP, Mallick A, Gandhi PU, Ibrahim NE, Simon ML, et al. Incident Type 2 myocardial infarction in a cohort of patients undergoing coronary or peripheral arterial angiography. *Circulation*. 2017;135:116–127. doi: 10.1161/CIRCULATIONAHA.116.023052
9. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology/American College of Cardiology/American Heart Association /World Heart Federation Task Force for the Universal Definition of Myocardial I. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264. doi: 10.1016/j.jacc.2018.08.1038
10. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2012;2013:1–150. doi: 10.1038/kisup.2012.73
11. Chalikias G, Drosos I, Tziakas DN. Contrast-induced acute kidney injury: an update. *Cardiovasc Drugs Ther*. 2016;30:215–228. doi: 10.1007/s10557-015-6635-0
12. Parco C, Brockmeyer M, Kosejian L, Quade J, Tröstler J, Bader S, Lin Y, Sokolowski A, Hoss A, Heinen Y, et al. National Cardiovascular Data Registry-Acute Kidney Injury (NCDR) vs. Mehran risk models for prediction of contrast-induced nephropathy and need for dialysis after coronary angiography in a German patient cohort. *J Nephrol*. 2021;34:1491–1500. doi: 10.1007/s40620-021-01124-9
13. Huang C, Li S-X, Mahajan S, Testani JM, Wilson FP, Mena CI, Masoudi FA, Rumsfeld JS, Spertus JA, Mortazavi BJ, et al. Development and validation of a model for predicting the risk of acute kidney injury associated with contrast volume levels during percutaneous coronary intervention. *JAMA Netw Open*. 2019;2:e1916021. doi: 10.1001/jamanetworkopen.2019.16021
14. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Weintraub WS, Curtis JP, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc*. 2014;3:e001380. doi: 10.1161/JAHA.114.001380
15. Scatena M, Liaw L, Giachelli CM. Osteopontin: a multifunctional molecule regulating chronic inflammation and vascular disease. *Arterioscler Thromb Vasc Biol*. 2007;27:2302–2309. doi: 10.1161/ATVBAHA.107.144824
16. Xie Y, Sakatsume M, Nishi S, Narita I, Arakawa M, Gejyo F. Expression, roles, receptors, and regulation of osteopontin in the kidney. *Kidney Int*. 2001;60:1645–1657. doi: 10.1046/j.1523-1755.2001.00032.x
17. Wesson JA, Johnson RJ, Mazzali M, Beshensky AM, Stietz S, Giachelli C, Liaw L, Alpers CE, Couser WG, Kleinman JG, et al. Osteopontin is a critical inhibitor of calcium oxalate crystal formation and retention in renal tubules. *J Am Soc Nephrol*. 2003;14:139–147. doi: 10.1097/01.ASN.0000040593.93815.9D
18. Kaleta B. The role of osteopontin in kidney diseases. *Inflamm Res*. 2019;68:93–102. doi: 10.1007/s00011-018-1200-5
19. Lorenzen JM, Hafer C, Faulhaber-Walter R, Kumpers P, Kielstein JT, Haller H, Fliser D. Osteopontin predicts survival in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26:531–537. doi: 10.1093/ndt/gfq498
20. Bagshaw SM, Bellomo R. Cystatin C in acute kidney injury. *Curr Opin Crit Care*. 2010;16:533–539. doi: 10.1097/MCC.0b013e32833e8412
21. Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R, Castaldo D, De Micco F, Ricciardelli B, Colombo A. Cystatin C and contrast-induced acute kidney injury. *Circulation*. 2010;121:2117–2122. doi: 10.1161/CIRCULATIONAHA.109.919639
22. Soto K, Coelho S, Rodrigues B, Martins H, Frade F, Lopes S, Cunha L, Papoila AL, Devarajan P. Cystatin C as a marker of acute kidney injury in the emergency department. *Clin J Am Soc Nephrol*. 2010;5:1745–1754. doi: 10.2215/CJN.00690110
23. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human

renal proximal tubule injury. *Kidney Int*. 2002;62:237–244. doi: 10.1046/j.1523-1755.2002.00433.x
24. Sabbisetti VS, Waikar SS, Antoine DJ, Smiles A, Wang C, Ravisankar A, Ito K, Sharma S, Ramadesikan S, Lee M, et al. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. *J Am Soc Nephrol*. 2014;25:2177–2186. doi: 10.1681/ASN.2013070758
25. Geng J, Qiu Y, Qin Z, Su B. The value of kidney injury molecule 1 in predicting acute kidney injury in adult patients: a systematic review and Bayesian meta-analysis. *J Transl Med*. 2021;19:105. doi: 10.1186/s12967-021-02776-8
26. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol*. 2005;16:3046–3052. doi: 10.1681/ASN.2005030236
27. Cook NR. Quantifying the added value of new biomarkers: how and how not. *Diagn Progn Res*. 2018;2:14. doi: 10.1186/s41512-018-0037-2
28. Pepe MS, Fan J, Feng Z, Gerds T, Hilden J. The Net Reclassification Index (NRI): a misleading measure of prediction improvement even with independent test data sets. *Stat Biosci*. 2015;7:282–295. doi: 10.1007/s12561-014-9118-0

Supplemental Material

Table S1. Assigned integer score based on CA-AKI risk model.

Variable	Integer Score
Presentation	
Asymptomatic/stable angina	0
Unstable Angina	2
NSTEMI	4
STEMI	8
eGFR, ml/min per 1.73 m^2	
≥60	0
30-59	1
<30	4
Left ventricular ejection fraction < 40%	2
Diabetes	
No diabetes	0
Non-insulin-treated	1
Insulin treated	2
Hemoglobin < 11 mg/dl	1
Basal glucose ≥ 150 mg/dl	1
Heart failure on presentation	1
Age > 75 years	1
Osteopontin ≥ 236 pg/mL	4
Cystatin C ≥ 0.92 mg/L	4

NSTEMI=non-ST-elevation myocardial infarction. STEMI=ST-elevation myocardial infarction. eGFR=estimated glomerular filtration rate, KIM-1: kidney injury molecule-1

Figure S1. CONSORT Diagram for the present analysis.

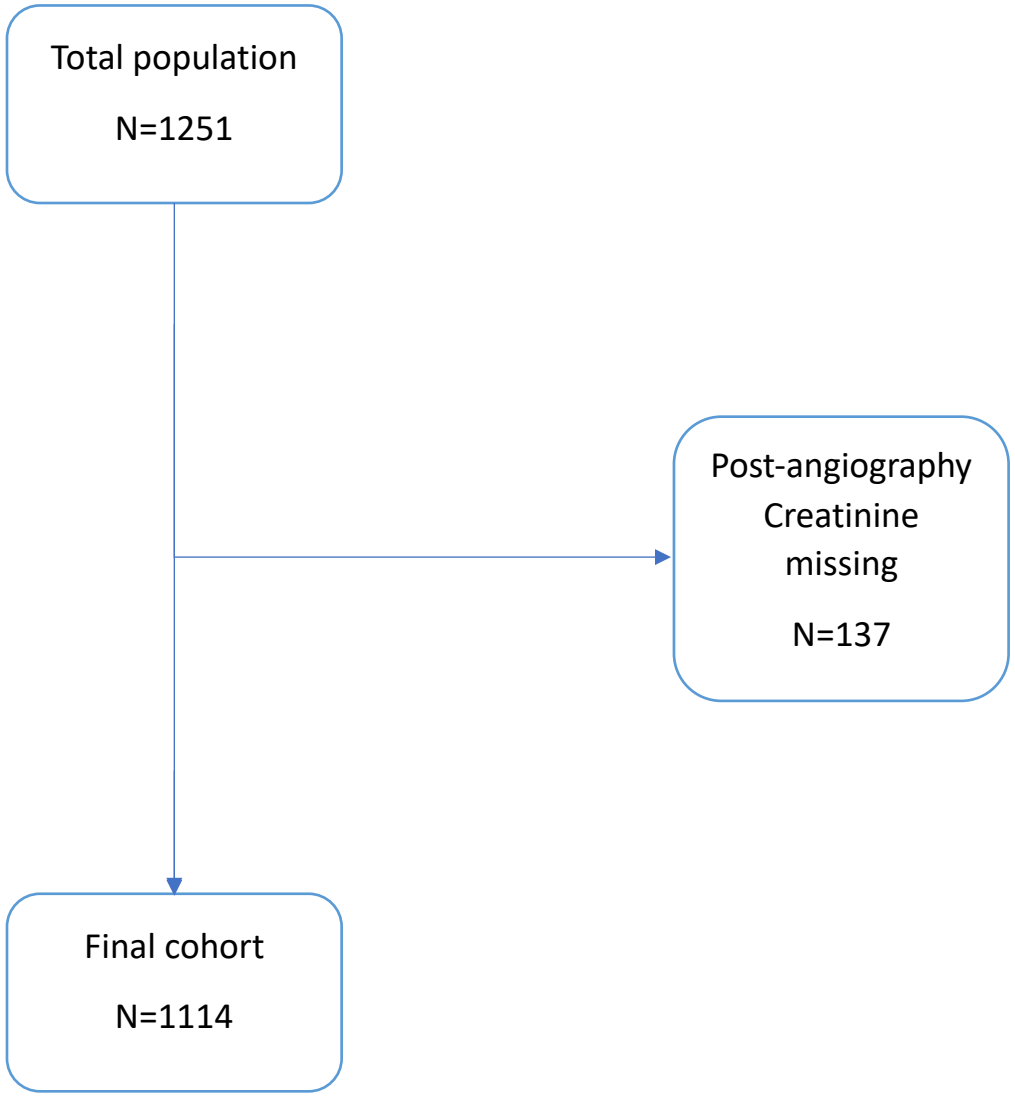
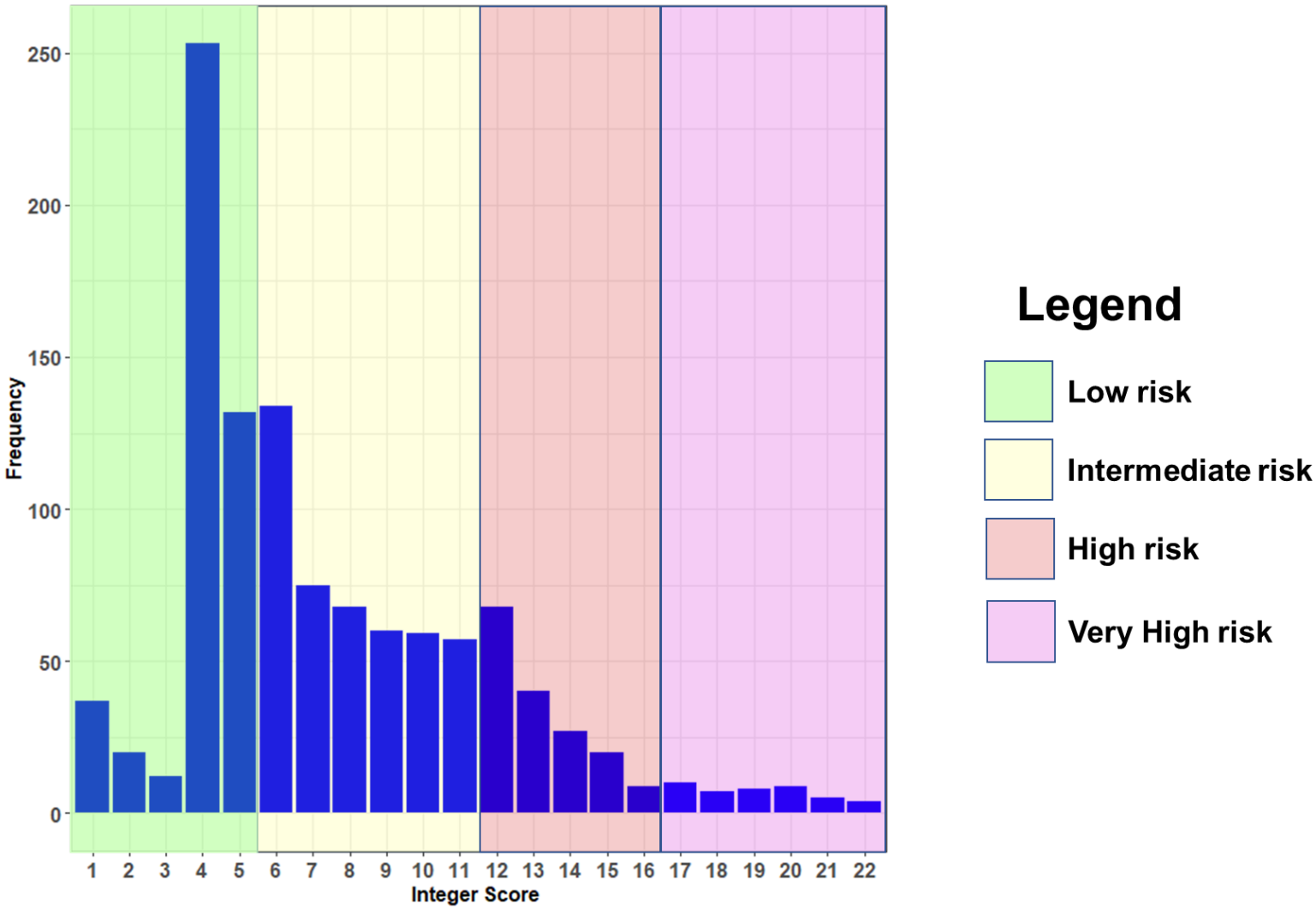


Figure S2. Distribution of CA-AKI integer score among study participants.



Quartiles for the score are indicated.