Clinical Cancer Research

# KIM-1 as a Blood-Based Marker for Early Detection of Kidney Cancer: A Prospective Nested Case–Control Study

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## Abstract

**Purpose:** Renal cell carcinoma (RCC) has the potential for cure with surgery when diagnosed at an early stage. Kidney injury molecule-1 (KIM-1) has been shown to be elevated in the plasma of RCC patients. We aimed to test whether plasma KIM-1 could represent a means of detecting RCC prior to clinical diagnosis.

**Experimental Design:** KIM-1 concentrations were measured in prediagnostic plasma from 190 RCC cases and 190 controls nested within a population-based prospective cohort study. Cases had entered the cohort up to 5 years before diagnosis, and controls were matched on cases for date of birth, date at blood donation, sex, and country. We applied conditional logistic regression and flexible parametric survival models to evaluate the association between plasma KIM-1 concentrations and RCC risk and survival.

**Results:** The incidence rate ratio (IRR) of RCC for a doubling in KIM-1 concentration was 1.71 [95% confidence interval (CI), 1.44–2.03, $P = 4.1 \times 10^{-23}$], corresponding to an IRR of 63.3 (95% CI, 16.2–246.9) comparing the 80th to the 20th percentiles of the KIM-1 distribution in this sample. Compared with a risk model including known risk factors of RCC (age, sex, country, body mass index, and tobacco smoking status), a risk model additionally including KIM-1 substantially improved discrimination between cases and controls (area under the receiver-operating characteristic curve of 0.8 compared with 0.7). High plasma KIM-1 concentrations were also associated with poorer survival ($P = 0.0053$).

**Conclusions:** Plasma KIM-1 concentrations could predict RCC incidence up to 5 years prior to diagnosis and were associated with poorer survival. *Clin Cancer Res; 24(22); 5594–601. ©2018 AACR.*

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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## Translational Relevance

Incidence of renal cell carcinoma (RCC) is rising, and although patients diagnosed with localized RCC (stages I and II) are commonly cured following nephron-sparing nephrectomy as the sole treatment, tumors that invade local tissues (stage III) or with distant metastasis (stage IV) have poor prognoses, with 5-year relative survival rates of about 50% and 10%, respectively. Identifying a sensitive and specific tumor marker that can detect early-stage RCC would have strong potential to improve the overall survival for RCC. There is currently no known blood-based biomarker that is predictive of future RCC diagnosis. We show that plasma concentrations of kidney injury molecule 1 (KIM-1) can predict incidence of RCC up to 5 years prior to diagnosis in a population-based cohort, and that prediagnostic KIM-1 is strongly predictive even among cases with good prognosis. Thus, KIM-1 has the potential to increase the proportion of cases diagnosed with localized, curable disease.

## Introduction

Kidney cancer is estimated to cause more than 140,000 deaths each year worldwide, and approximately 330,000 new diagnoses are recorded annually (1). The large majority (over 80%) are renal cell carcinomas (RCC). Patients diagnosed with localized RCC (stages I and II) are commonly cured following nephron-sparing nephrectomy as the sole treatment, with limited long-term side effects. Tumors that invade local/regional tissues (stage III) or with distant metastasis (stage IV) have poor prognoses, with 5-year survival rates of about 50% and 10%, respectively (2). The majority of early-stage tumors are asymptomatic and incidentally detected via imaging exams for a range of medical conditions and symptoms. There is currently no recommended screening practice for primary RCC in people who are not known to carry gene variants associated with an increased risk of the disease. With this background, identifying a sensitive and specific tumor marker that can detect early-stage RCC would have strong potential to improve the overall survival for RCC. There is currently no known blood-based biomarker that is predictive of future RCC diagnosis.

Kidney injury molecule-1 (KIM-1) is a protein that is normally expressed at very low levels in the kidney and in any other normal tissue, but is upregulated in injured renal tubule cells (3, 4). The ectodomain of KIM-1 undergoes cleavage and can be detected in urine and blood (5, 6). It was previously shown in urine (7–9) and more recently in plasma (Sabbisetti and colleagues, under review) through case–control studies that concentrations of KIM-1 are drastically elevated at the time of diagnosis in clear cell RCC (ccRCC). Using healthy controls as the reference, Sabbisetti and colleagues demonstrated that the area under the receiver-operating characteristic curve (AUC) afforded by plasma KIM-1 alone was 0.96 [95% confidence interval (CI), 0.93–0.99]. In a complementary analysis, they observed a significant decrease in plasma KIM-1 concentrations comparing post- to prenephrectomy plasma sample pairs in 13 ccRCC cases. These two observations suggest that KIM-1 plasma concentrations may be a sensitive and specific biomarker for RCC diagnosis, as well as specific to the presence of the tumor (decrease of the concentration after surgical removal of the tumor). However, it is not known whether KIM-1 is detectable prior to RCC diagnosis.

In this study, we aimed to assess whether plasma KIM-1 concentrations measured in blood samples collected up to 5 years prior to diagnosis were associated with risk of subsequent RCC diagnosis, and to explore the potential of using KIM-1 as an early detection biomarker of RCC in order to improve survival.

## Materials and Methods

### Study sample

We used plasma samples from the European Prospective Investigation into Cancer and nutrition (EPIC). The EPIC study is an ongoing multicenter prospective cohort that recruited 521,330 participants between 1992 and 2000 from 23 centers across 10 countries in Europe, of whom 385,747 donated a blood sample at study recruitment. The current study involved EPIC participants from nine countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, the United Kingdom, and Spain). Details on recruitment procedures, collection of questionnaire and anthropometric data, and blood sample collection and storage have been described in detail elsewhere (10). The study was conducted in accordance with the Declaration of Helsinki. Ethical review boards of the International Agency for Research on Cancer (IARC) and all local institutions where participants were recruited gave approval for the study, and all participants gave written informed consent for data collection and storage, as well as individual follow-up

A nested case–control series was defined within the cohort as detailed elsewhere (11). In brief, for each incident RCC case (defined as C64.9, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)) that was histologically confirmed, one control was randomly chosen from risk sets consisting of all cohort members alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index RCC cancer case. Matching criteria were country, sex, date of blood collection ($\pm$1 month, extended to $\pm$5 months for sets without available controls), and date of birth ($\pm$1 year, extended to $\pm$ 5 years).

For this study, we included every case that had entered the cohort and donated blood up to 5 years before being diagnosed with RCC. In total, 190 cases (152, 80% ccRCC) and 190 controls were included in the study. Baseline characteristics of the study participants by case–control status are available in Supplementary Table S1.

### Biomarker measurement

Plasma concentrations of KIM-1, as well as tumor necrosis factor receptors 1 and 2 (TNFR1 and TNFR2) as markers of chronic inflammation, were measured using a microbead-based assay as described previously (5). Samples were diluted 10-fold in sample diluent buffer (0.1 mol/L HEPES, 0.1 mol/L NaCl, 0.1% Tween-20 and 1% BSA; pH 7.4; filter sterilized), and 30 μL of diluted sample, recombinant standards, and internal control samples were incubated with ~6,000 microbeads that were coupled with KIM-1, TNFR1, and TNFR2 capture antibodies for 1 hour (R&D Systems). After incubation, microbeads were washed 3 times with PBST and incubated with corresponding detection antibodies (R&D Systems) for 45 minutes. After incubation, beads were washed 3 times with PBS-Tween and incubated with Streptavidin-PE (Invitrogen) for 15 minutes. The signal from the

fluorochrome, which is directly proportional to the amount of antigen bound at the microbead surface, was captured using the Bio-Plex system (Bio-Rad). The lower level of detection (LLOD) for KIM-1, TNFR1, and TNFR 2 were 1.02 pg/mL, 0.67 pg/mL, and 0.17 pg/mL, respectively, and this value was assigned to all samples where analytes were not detected. As a marker of kidney function, we used creatinine mass spectrometry measurements (12) conducted in the context of previous studies (11).

**Statistical analysis**

To evaluate the association between KIM-1 concentrations and RCC risk, we calculated odds ratios and 95% CIs using conditional logistic regression, conditioning on the matched case sets. These odds ratios estimate incidence rate ratios (IRR) given the incidence density matched design of our study. We estimated IRRs for a doubling in KIM-1 concentrations by including a $\log_2$ transformed continuous variable in the logistic regression models. To put the IRRs in context, we contrasted the 80th and 20th percentiles of the KIM-1 concentrations in EPIC, estimated by weighting each observation according to its probability of being included in the nested case–control sample. We evaluated the extent to which the association of KIM-1 with RCC risk was modified by other risk factors, including age at diagnosis (both as a continuous variable and in groups defined prior to analysis, chosen to ensure a sufficient number of cases in each group: <55; ≥55 and <65; ≥65), sex, tobacco smoking, hypertension, diabetes, and body mass index (BMI), by using the likelihood ratio test on interactions fitted between KIM-1 and each covariate. One participant was missing BMI, so models including BMI include 189 cases. Analyses with grouped continuous age at diagnosis yielded substantively similar results, so for convenience of reporting we present results by age groups. Similarly, we assessed potential heterogeneity by histologic type (ccRCC or others/missing) and time since blood draw (grouped as less than 2 years vs. 2–5 years) by fitting interaction terms between KIM-1 and variables for histologic type or time since blood draw. For these analyses by histologic type and time-to-diagnosis, matched controls were given the same value of the covariate as their index case to allow estimation of stratum-specific estimates and tests of interaction, because histologic type and time-to-diagnosis are not defined for participants not diagnosed with RCC. These interaction tests have limited statistical power compared with the test of the main effect, but taken in context of a qualitative assessment of stratum-specific estimates, they provide an indication as to whether there is any substantial heterogeneity of the association by individual-level factors. Deviation from log-linear trend was tested by comparing the log-linear model with a 3 degree-of-freedom restricted cubic spline model using the likelihood ratio test.

The associations between concentrations of KIM-1 with those of TNFR1, TNFR2, and creatinine were assessed by correlation. Additionally, the three measures were added to the risk model with KIM-1 to evaluate whether they affected the KIM-1 risk estimate.

We used flexible parametric survival models (13) to estimate the 5-year absolute risk of RCC as a function of KIM-1 concentration, age, sex, BMI, and smoking status (never, ex-, and current smoker), averaged across country of recruitment. These models were fitted to the nested case–control sample, with each participant's contribution to the likelihood weighted by the probability that they were selected into the nested case–control sample (14). The key advantage of flexible parametric survival models is that they use restricted cubic splines to model the baseline cumulative hazard function, and can thus accommodate a variety of different functional forms, which can then be used to directly obtain predicted risks from the fitted model. We used restricted cubic splines with 3 degrees of freedom to model the baseline cumulative hazard of RCC as a function of time since blood draw. The model's ability to discriminate those at high and low risk was assessed using the AUC and was compared with a base model which included all predictors except for KIM-1 concentration.

We further evaluated whether prediagnostic KIM-1 concentrations were associated with the risk of death after RCC diagnosis (overall survival) among the cases by fitting flexible parametric survival models (13). These models used restricted cubic splines with 3 degrees of freedom to model the baseline cumulative hazard as a function of time since diagnosis, with these hazards allowed to vary by age at diagnosis. Analyses were conducted with R version 3.4.3 (15) and Stata version 12.1 (Stata Corporation).

## Results

KIM-1 was detected in 177 cases (93%) and 133 controls (70%; Table 1). In samples with detectable levels of KIM-1, the median concentrations were 149 and 59 pg/mL in cases and controls, respectively.

The IRR of RCC for a doubling in KIM-1 concentration, conditioning on age, sex, and country, was 1.71 (95% CI: 1.44–2.03; $P = 4.1 \times 10^{-23}$). Further adjusting for BMI and smoking status at baseline did not much change the estimate (IRR, 1.72; 95% CI, 1.44–2.06; $P = 1.1 \times 10^{-21}$). We found no substantial evidence for deviation from the log-linear trend ($P$ for test of nonlinearity = 0.13; Supplementary Fig. S1). In the context of the distribution of KIM-1 concentrations in EPIC, this translates to an IRR of 63.3 (95% CI, 16.2–246.9) when comparing the 80th percentile (199.04 pg/mL) to the 20th percentile (undetected concentration). Figure 1 shows the IRRs for a doubling in KIM-1 concentration by individual characteristics. We found little evidence that the adjusted IRR of 1.72 varied by smoking status, sex, age at baseline, BMI, history of hypertension or diabetes ($P$ for heterogeneity above 0.27). The association was strong for both ccRCC and RCC of other or missing subtype, with IRR estimates of 1.82 (95% CI, 1.47–2.26) and 1.48 (95% CI, 1.11–1.98), respectively. The association of KIM-1 with risk was similar for cases diagnosed within 2 years after blood draw (IRR, 1.82; 95% CI, 1.38–2.50) and cases diagnosed between 2 and 5 years after blood draw (IRR, 1.63; 95% CI, 1.30–2.05; $P$ for heterogeneity = 0.49). In the absence of complete information on stage for the RCC cases, we conducted a sensitivity analysis in which 72 cases who did not survive at least 5 years after their diagnosis were excluded, along with their matched controls. Considering only the remaining 118 cases with good prognosis, KIM-1 was still strongly associated with risk (IRR, 1.61; 95% CI, 1.31–1.98, $P = 4.5 \times 10^{-11}$). Plasma concentrations of creatinine and TNF receptors were not found to be strongly correlated with KIM-1 concentrations (Supplementary Fig. S2). Their addition to the model also did not much affect the association between KIM-1 concentration and RCC risk (IRR, 1.74; 95% CI, 1.45–2.08).

Predicted probabilities of being diagnosed with RCC in the 5 years are plotted against KIM-1 plasma concentrations in Figure 2, based on the weighted full model that included age, sex, country, BMI, and tobacco smoking status in addition to KIM-1. As

**Table 1.** Distribution of plasma KIM-1 concentrations (pg/mL) by case–control status, and by histologic subtypes of RCC

| Statistics | Controls ($n = 190$) | RCC cases overall ($n = 190$) | ccRCC cases ($n = 152$) |
|---|---|---|---|
| $N_{detected}$ (%) | 133 (70.0) | 177 (93.2) | 141 (92.8) |
| Median[a] | 59 | 149 | 149 |
| 5$^{th}$ percentile[a] | 4 | 15 | 21 |
| 95$^{th}$ percentile[a] | 351 | 3,090 | 3,090 |
| Range[a] | 1.48–8,253 | 1.48–79,472 | 1.48–79,472 |

[a]Among detected samples. LLOD: 1.02 pg/mL.

compared with a base model that included these predictors (AUC, 0.71; 95% CI, 0.65–0.77), adding KIM-1 concentration in the model significantly improved the discrimination (AUC, 0.80; 95% CI, 0.75–0.85); Wald test of KIM-1 coefficient $P = 5.3 \times 10^{-6}$, $P$ for difference in AUC, 0.002; Fig. 2). Adding KIM-1 to the model approximately doubled the sensitivity as compared with the base model: for a specificity of 75%, the sensitivity increased from 42% to 76%, and for a specificity of 95%, the sensitivity increased from 21% to 54%. Absolute risk of an RCC diagnosis as a function of follow-up time is plotted in Figure 3, for different ages at blood draw and example KIM-1 concentrations. Based on the estimated baseline incidence rate averaged across the EPIC participating countries, and for male current smokers with a BMI of 30 kg/m$^2$ as an example, the 5-year risk of RCC was below 0.2% for those with KIM-1 of 50 pg/mL, regardless of age at blood draw. A KIM-1 concentration of 800 pg/mL, in contrast, implied a 5-year risk of 1.0% (95% CI, 0.4–2.4) for those with blood drawn at age 60 years, and 1.4% (95% CI, 0.5–3.8) for those ages 70 years at blood draw.

During a median follow-up of 7.8 years after diagnosis, 88 of the 190 RCC cases had died (65 of whom had RCC being reported as the sole originating cause of death). The median survival time among those who died was 1 year. We found evidence of a nonlinear association between KIM-1 concentration and risk of death among RCC cases ($P$ for test of nonlinearity = 0.07) and used flexible nonlinear (3 degrees of freedom) models to estimate hazard ratios (HR) and 95% CIs (Fig. 4A). Using these models and 50 pg/mL for the reference KIM-1 concentration, we estimated HRs of death for all causes at 1.45 (95% CI, 1.12–1.86) for 100 pg/mL, 2.38 (95% CI, 1.32–4.27) for 200 pg/mL, 3.17 (95% CI, 1.51–6.65) for 400 pg/mL, and 3.29 (95% CI, 1.61–6.74) for 800 pg/mL (overall $P$: 0.0053). Figure 4 B depicts the overall survival probabilities after RCC diagnosis for three values of KIM-1 concentration and by age at diagnosis. For an individual diagnosed with RCC between the ages of 55 and 65 years, the 5-year survival probability was 0.74 given a KIM-1 concentration of 50 pg/mL, and 0.65 or below given a concentration of 200 pg/mL or greater.

## Discussion

This study demonstrated that plasma KIM-1 concentrations are strongly associated with the risk of being diagnosed with RCC in

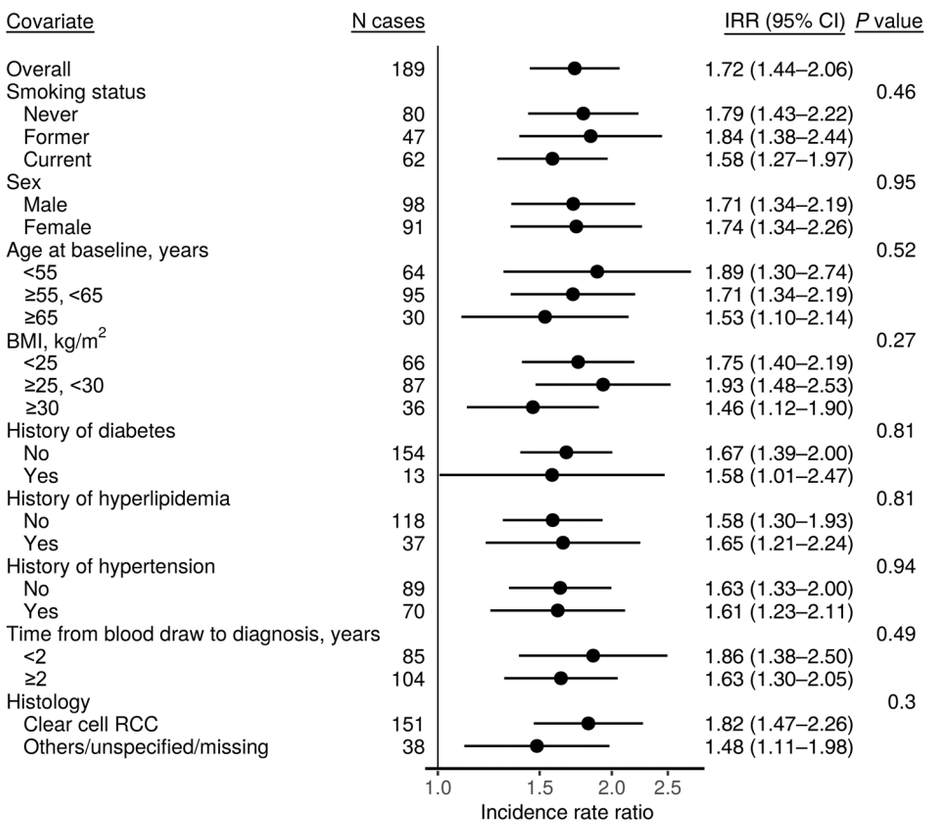


**Figure 1.**
RCC incidence rate ratios for a doubling in KIM-1 concentration, overall and by individual characteristics. Rate ratios were estimated using conditional logistic regression models fitted to the matched case–control sets (matching criteria: date at blood draw, date of birth, sex, country) and were further adjusted for BMI and smoking status. The rate of RCC incidence was increased with higher concentrations of KIM-1. This association did not vary by individual characteristics or time between blood draw and RCC diagnosis. The $P$ values are from likelihood ratio tests of the interaction terms, which test the null hypothesis of no differences among levels of the risk factors.

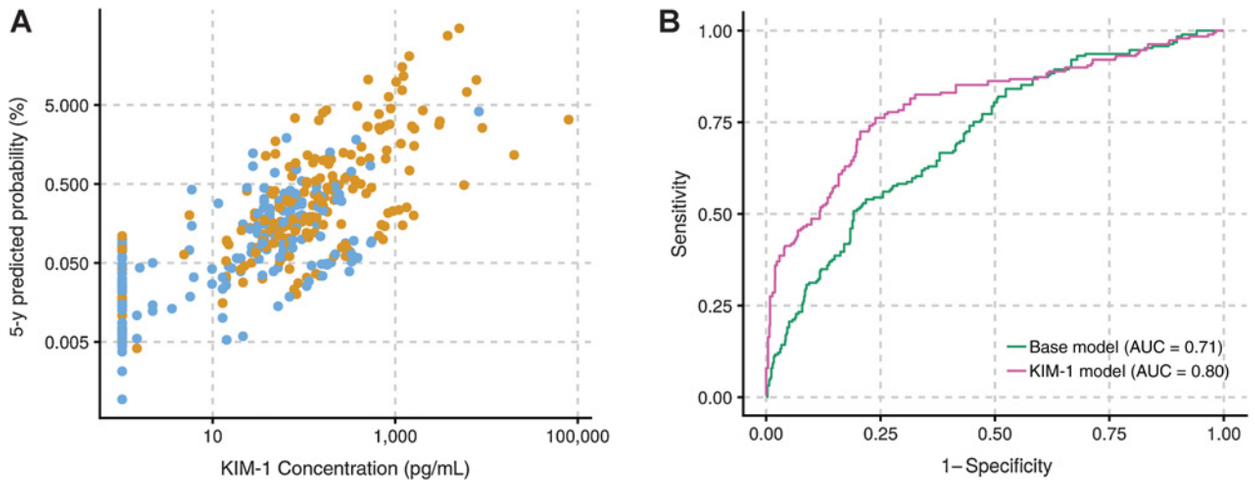


**Figure 2.**

**A,** Predicted probabilities of being diagnosed with RCC within 5 years by KIM-1 plasma concentrations. Cases are represented by orange dots and controls by blue dots. **B,** ROC curves depicting the ability of KIM-1 to improve the discrimination between cases and controls. Base model includes age, sex, country, BMI, and tobacco smoking status. Plasma KIM-1 concentrations are capable of improving the discrimination between those who go on to be diagnosed with RCC within 5 years and those who do not.

the following 5 years. We estimated that a concentration of about 200 pg/mL (80th percentile of plasma KIM-1 distribution in our sample) conferred a 63-fold higher risk when compared with undetectable plasma KIM-1 concentrations in the EPIC cohort. We also showed that prediagnostic elevated plasma KIM-1 concentrations were associated with higher risk of death in RCC cases.

This study was motivated by previous studies in which we showed that plasma KIM-1 was elevated in RCC patients at the time of diagnosis and that KIM-1 concentrations dropped after nephrectomy (Sabbisetti and colleagues under review). These findings led to the hypothesis that plasma KIM-1 is a biomarker that could predict the development of RCC. To our knowledge, this is the first time that KIM-1 has been assessed in prediagnostic samples.

The EPIC study is a large population-based prospective cohort study, wherein blood samples and questionnaire information were collected from participants at study entry who were subsequently followed for cancer outcome. This is an ideal setting to evaluate the association between plasma KIM-1 and RCC risk, i.e., for testing whether elevated plasma KIM-1 concentrations can be detected in participants from a general, nonclinical population prior to any cancer diagnosis. The principal limitation of our study is the lack of complete information on tumor stage, but we could circumvent this limitation to some degree by conducting analyses limited to cases with good prognosis who were likely to have been diagnosed at an early stage.

We found that plasma KIM-1 concentration substantially improved the discrimination between participants who were

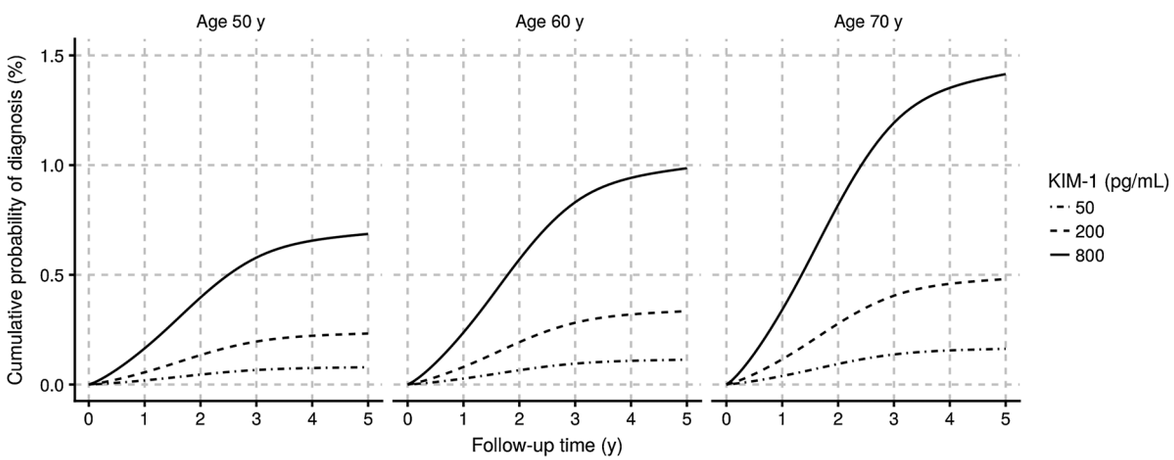


**Figure 3.**

Absolute risk of an RCC diagnosis as a function of follow-up time, for given ages and KIM-1 concentrations. Estimates are conditional on being male current smoker with a BMI of 30 kg/m$^2$, and the estimated baseline incidence rate of RCC averaging across EPIC participating countries. Absolute risk of RCC is substantially higher for those with high KIM-1 concentrations compared with those with lower concentrations. y, years.

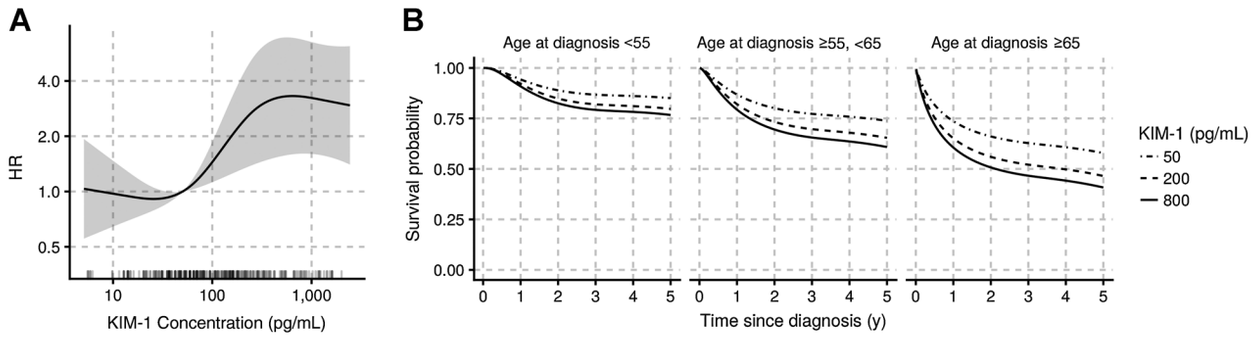


**Figure 4.**

**A,** Estimated HRs and 95% CIs for risk of death among RCC cases from flexible nonlinear (3 degrees of freedom) models. **B,** Estimated conditional survival functions by age at diagnosis and KIM-1 concentrations. KIM-1 was modeled using a 3 degree-of-freedom restricted cubic spline. The baseline hazard was separately modeled for each age group with a 3 degree-of-freedom restricted cubic spline. The rate of death increased with higher prediagnostic concentrations of KIM-1: death rates were over 3-fold higher for RCC cases with KIM-1 concentrations greater than 400 pg/mL, compared with those whose concentrations were at or below 50 pg/mL. y, years.

diagnosed with RCC within 5 years versus those were not, with an AUC of 0.80 as compared with 0.71 when only known RCC risk factors were included in the models. The improvement was particularly apparent in the higher range of specificity (Fig. 2B). An AUC of 0.80 is higher than the AUCs observed for any of the nine multivariable prediction models being evaluated in the context of lung cancer screening eligibility, which are in turn greater than established models for other cancers such as the Gail breast cancer risk prediction model (16). Further, we observed that a model including KIM-1 could achieve a sensitivity of 0.42 for a given specificity of 0.95, indicating that it may be substantially more sensitive for RCC detection than prostate-specific antigen (PSA) is for prostate cancer (17). As an example, we estimated the risk of being diagnosed with RCC during the following 5 years for a 70-year-old smoking man with KIM-1 concentrations of 800 pg/mL and BMI 30 kg/m$^2$ was 1.4% when averaging the baseline risk across EPIC participating countries. It reached 2.5% in Germany, where the highest incidence rates are found across EPIC participating countries (18). Thus, despite excellent discrimination, KIM-1 in combination with established risk factors is unlikely to be useful for early detection of RCC in a general population setting. We envisage that KIM-1 will be useful in settings where the risk of RCC is higher, such as patients undergoing abdominal CT scanning, where KIM-1 could be used to stratify risk of RCC. This will be particularly important given the rise of routine CT scans, and the strong association between the number of CT scans and number of nephrectomies performed at the regional level in the US, indicating a substantial burden of overdiagnosis (19).

This study focused on the first 5 years of follow-up, assuming that the potential utility of KIM-1 as a predictor of RCC would diminish as the time between blood draw and diagnosis increases. One unexpected finding was that the increase in risk associated with elevated KIM-1 concentrations did not vary with time: the risk was similarly high in cases diagnosed within 2 years of their plasma collection and in those diagnosed between 2 and 5 years after collection. This could potentially be explained by a large proportion of advanced-stage tumors at diagnosis, which were not clinically manifest at the time of blood draw. However, our analysis indicates that KIM-1 concentrations remain strongly associated with risk of RCC even when considering only those cases who survived for more than 5 years after their diagnosis. The fact that this association exists among those with good prognosis suggests that KIM-1 might be useful in predicting early-stage disease, for which definitive curative treatment is successful (20).

That KIM-1 concentrations are elevated in RCC cases at least up to 5 years before diagnosis, including cases with good prognosis (presumably diagnosed with early-stage tumors), also indicates that the natural history of the disease may extend well beyond 5 years. The window for early detection would then cover a substantial period of time. More research is also needed to fully understand the natural history of RCC and to estimate the prevalence of indolent tumors that are unlikely to progress, and for which detection and treatment would be unnecessary. Future research is necessary to investigate how long before RCC diagnosis KIM-1 is elevated, as well as whether KIM-1 becomes elevated prior to the initial neoplastic transformations in the kidney.

Most RCCs remain asymptomatic until an advanced stage, and many RCCs are diagnosed incidentally during routine imaging for unrelated examinations. Biomarkers of disease or risk could enable the identification of subsets of the population for whom screening for RCC via radiologic imaging may be feasible and effective. Aside from KIM-1, markers of chronic inflammation and hypoxia such as IL6, CAIX, and serum amyloid have also been described (21–25). We have also shown that vitamin B6 tends to be higher in patients with lower risk of RCC (11). More recently, circulating micro RNAs have been shown to be elevated in RCC (26, 27). Any biomarker or set of biomarkers will be most informative if they are not associated with risk or presence of other cancers, but to date, KIM-1 has not been evaluated in relation to risk of other cancers.

One possible caveat for the use of KIM-1 for detection of RCC is that it is also present in the setting of kidney injury which would potentially constitute false positives if KIM-1 was to be used as a screening tool. However, most patients who have an incidental diagnosis of localized RCC present with normal renal function, differentiating them from other renal diseases. Moreover, we studied creatinine levels as well as markers of systemic inflammation (TNF receptors), and inclusion of these factors did not affect the strong association between KIM-1 concentrations and risk of RCC.

In summary, we demonstrated that plasma KIM-1 is a promising candidate biomarker for RCC early detection, owing to its strong performance in predicting RCC in a general population cohort. Although predicted probabilities of RCC based on KIM-1 are likely to be too small to indicate its use in a general population setting, in a clinical setting KIM-1 has the potential to increase the proportion of cases diagnosed with localized, curable disease.

## Disclosure of Potential Conflicts of Interest

J.V. Bonventre is listed as an inventor of a patent regarding KIM-1 assigned to Partners Healthcare. No potential conflicts of interest were disclosed by the other authors.

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