Serum Protein Markers in Clear Cell Renal Cell Carcinoma

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ABSTRACT

BACKGROUND

Renal Cell Carcinoma (RCC) is one of the most frequently diagnosed malignancies, yet non-invasive biomarkers for early detection and prognosis in RCC remain scarce. This study aims to identify serum protein markers predictive of clear cell RCC (ccRCC) development and prognostic of survival outcomes.

METHODS

Using the UK Biobank, a prospective cohort of >500,000 individuals, we analyzed serum proteomic data from participants who developed ccRCC after serum collection (Group 2), those diagnosed prior to serum collection (Group 1), and controls (Group 3). Proteomic measurements were performed using the Olink Proximity Extension Assay (PEA). Cox proportional hazards regression models estimated hazard ratios (HRs) for cancer risk and survival, adjusting for age, sex, BMI, smoking status, and renal function. Kaplan-Meier survival analysis evaluated prognostic markers.

RESULTS: Five serum proteins—HAVCR1, REN, INHBB, NCR3LG1, and PGF—were significantly associated with future ccRCC development. HAVCR1 exhibited the strongest predictive performance (HR 5.1, 95% CI: 3.6–7.3, p<0.001; AUC 0.8756). Among all patients with ccRCC, NCR3LG1 (HR 2.6, 95% CI: 1.4–5.1, p<0.002), PGF (HR 2.2, 95% CI: 1.3–3.8, p<0.001), and GDF15 (HR 1.8, 95% CI: 1.1–2.8, p<0.02) were associated with reduced survival.

CONCLUSION

This study identifies HAVCR1 as a promising diagnostic biomarker for early ccRCC detection, with NCR3LG1, PGF, and GDF15 serving as potential prognostic markers. Further validation in independent cohorts is needed to facilitate clinical translation into diagnostic and prognostic tools for ccRCC.

KEYWORDS: Renal Cell Carcinoma, Serum Biomarkers, Proteomics, HAVCR1/KIM-1

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INTRODUCTION

Renal Cell Carcinoma (RCC) is among the most frequently diagnosed malignancies in both genders with over 81,000 estimated cases in 2024[1]. Incidence of renal mass detection has steadily increased over the past decades, largely due to increased cross sectional imaging revealing incidental renal masses at a lower stage[2]. Despite improved early detection of RCC, imaging remains cost-prohibitive and is not without risk to the patient, therefore image based screening is not recommended for average risk patients. While non-invasive diagnostic and prognostic biomarkers for other urologic cancers including PSA for prostate cancer and AFP and βHCG in testes cancer have been previously recognized and validated, accurate and reliable markers for RCC have proven much more elusive with no clinically actionable markers identified at present.[3] Though many potential biomarkers have been investigated in RCC in the past, most have been targeted towards predicting response to the armamentarium of RCC treatment options rather than focusing on use for cancer screening or detection of recurrence. While cell-free and circulating tumor DNA appear promising in early diagnosis or recurrence detection in RCC, they have yet to be adopted into

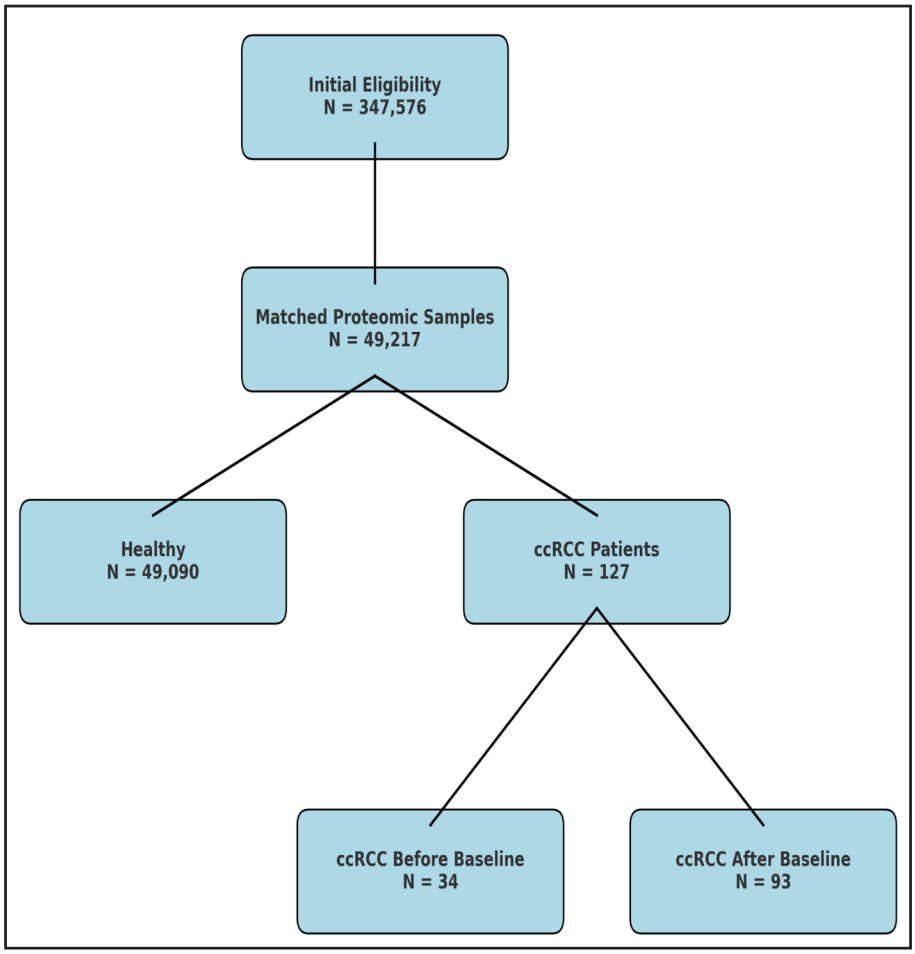

Figure 1. Flowchart of patient cohorts.

Characteristic	Group 1 (Had RCC at Baseline)	Group 2 (Developed RCC Later)
Total Patients	34	93
Mean Age at Recruitment (±SD)	61.2 (6.4)	59.3 (7.0)
Sex (Male/Female)	26 / 8	54 / 39
Mean BMI (±SD)	30.0 (5.5)	29.4 (4.8)
Smoking: Never (%)	9 (26.5%)	28 (30.1%)
Smoking: Current (%)	25 (73.5%)	65 (69.9%)
GFR (Creatinine, Mean ± SD)	60.1 (20.0)	84.2 (14.9)
Time to Diagnosis (Mean ± SD)	3.6 (3.7)	-6.5 (3.6)

Table 1: Patient characteristics by cohort. BMI = body mass index (measured in k/m^2); GFR = glomerular filteration rate (measured in mL/min/1.73m^3); SD= standard deviation.

practice due to the low levels of DNA shedding that are the hallmark of the disease. Additionally, the costliness of these tests may pose a barrier to widespread clinical use.

A recent publication by Papier *et al.* examined proteomic risk factors for 19 different cancers including kidney cancer utilizing data from the UK Biobank (UKBB). While the authors identified 51 proteins associated with kidney cancer risk, these proteins were not stratified by histologic subtype. As kidney cancer is known to be a disease with significant heterogeneity, biomarkers that are powerful predictors for one subtype of kidney cancer will not necessarily be useful in others[4]. With this in mind, we hypothesized that specific serum protein biomarkers can differentiate patients who later develop clear cell RCC (ccRCC) from those who do not, and help predict outcomes in patients who have been diagnosed with ccRCC. To test this hypothesis, our study utilized data from the UKBB to identify diagnostic serum protein biomarkers in patients who did not have ccRCC at the time of serum sampling but later developed it. We also examined serum samples of all patients diagnosed with ccRCC to identify potential prognostic markers using proteomic analysis.

MATERIALS AND METHODS

To support our aims, we conducted a population-level examination of serum proteomic markers associated with ccRCC using data from the UKBB, a large population based prospective cohort of over 500,000 individuals ages 40-69 recruited between 2006-2010 in the United Kingdom. All participants completed baseline assessments, including demographic and lifestyle data (e.g., BMI, smoking status) and physical measurements (Table 1). Non-fasting blood samples were also collected at baseline, which were processed into plasma and stored at −80 °C. As part of the UK Biobank Pharma Proteomics Project (UKB-PPP), protein measurements were performed using the Olink Proximity Extension Assay (PEA).

The relative abundance of proteins was quantified across four 384-plex panels designed to profile inflammatory, oncologic, cardiometabolic, and neurologic markers. These measurements, expressed as log2-transformed normalized protein expression (NPX) values, provided a comprehensive proteomic landscape for subsequent analyses. Cancer incidence and mortality data were obtained via linkage to national registries (NHS Digital for England and Wales, and the NHS Central Register for Scotland), and participants were followed until December 31, 2020, in England and Wales or November 30, 2021, in Scotland, or until death, withdrawal of consent, or emigration. For the observational analyses, kidney cancer (ICD codes C64–C65) was the endpoint, further stratified to ccRCC when histologic data permitted. (Figure 1) Our patient cohorts included individuals with established RCC that had been diagnosed before serum collection (Group 1) vs. patients without ccRCC at the time of recruitment who devel-

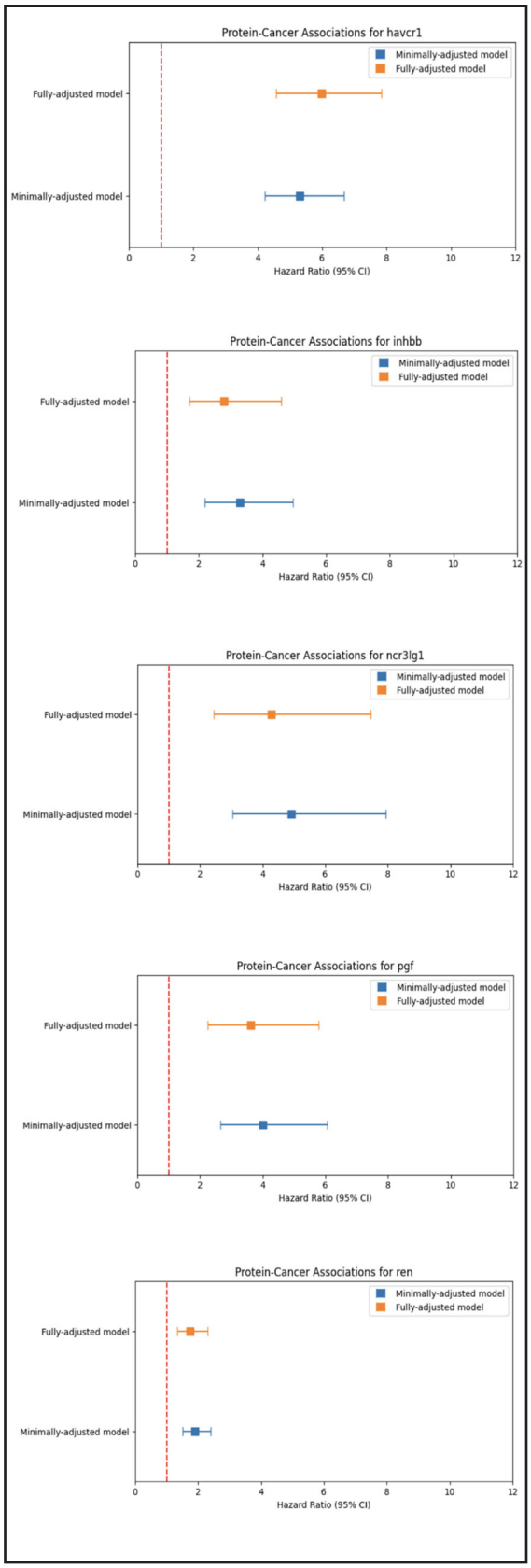

Figure 2: Protein-Cancer Associations for proteins of interest in previously undiagnosed ccRCC patients.

oped the disease later (Group 2) vs a group of healthy controls (Group 3). All were matched by age, sex, and BMI. We estimated hazard ratios (HRs), 95% confidence intervals (CI), and survival while adjusting for the aforementioned covariates using Cox proportional regression models. We investigated protein and ccRCC cancer-risk associations to examine the effects of reverse causality and conducted analyses to generate area under the curve (AUC) values to evaluate diagnostic performance of biomarkers. Finally, we utilized Kaplan-Meier curves to estimate survival rates based on high or low serum concentrations of proteins of interest.

Study Design & Data Selection

This study was conducted using the UKBB, a population-based cohort of approximately 500,000 individuals aged 40-69 recruited between 2006-2010. Participants completed baseline assessments, including demographic and lifestyle data (e.g., BMI, smoking status), physical measurements, and blood sampling. Our analysis further focused on individuals with available multiplex proteomic data performed using Olink Proximity Extension Assay (PEA) as part of the UK Biobank Pharma Proteomics Project (UKB-PPP),

To be included in the analysis, participants needed complete data on age, sex, BMI, smoking status, and serum creatinine for calculating estimated glomerular filtration rate (eGFR) using the CKD-EPI formula. From the full cohort, of 347,567 patients, 346,432 individuals were identified who had complete phenotypic data and serum creatinine. Of these, 49,217 also had proteomic data available. Only individuals with valid proteomic data (non-missing NPX values) were retained. Individuals with missing or unusable data on demographics or proteomics were excluded from the study.

Renal cell carcinoma (RCC) cases were identified using ICD-10 codes C64 and C65. Among the 127 patients diagnosed with clear cell RCC, 34 were diagnosed at or before serum collection, while 93 were initially cancer-free and developed the disease later. The remaining participants formed the healthy control group (n= 49,090).

Preprocessing & Quality Control:

We performed extensive preprocessing to ensure that the data were of high quality for analysis. Proteomic data were generated using Olink's multiplex PEA, which produce Normalized Protein eXpression (NPX) values on a relative log2-like scale. These proteomic values were integrated with the UKBB phenotype data based on participant identifiers. Any discrepancies, such as duplicate records or inconsistent IDs, were reviewed and resolved or discarded.

Proteins with more than

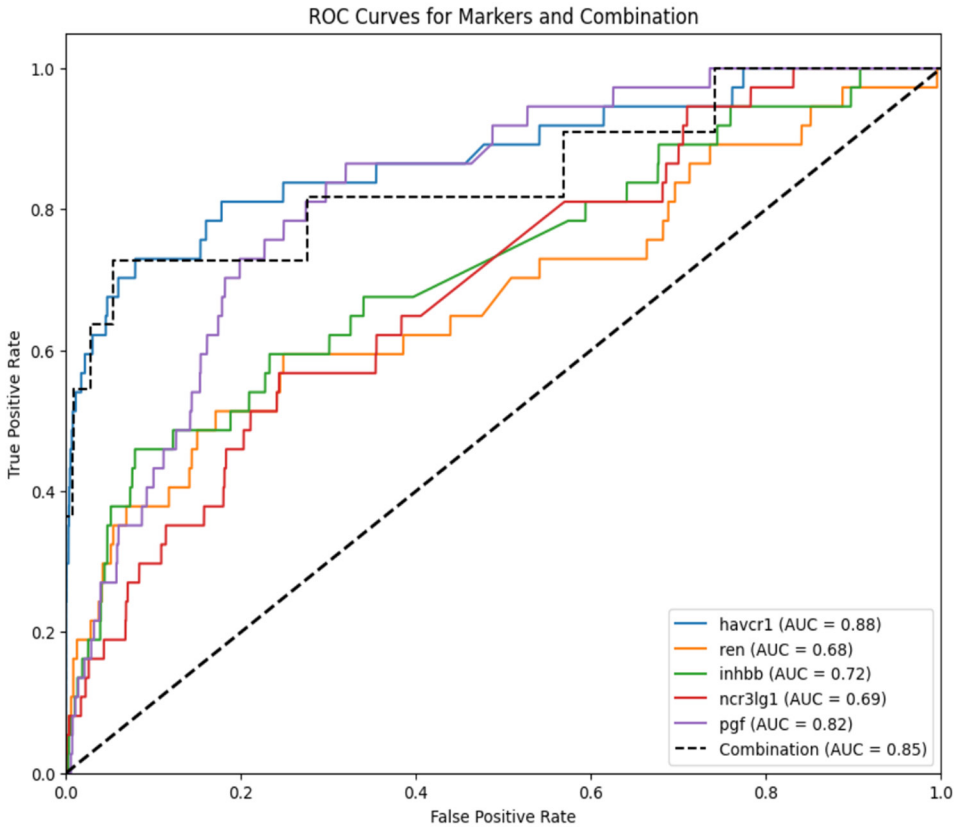

Figure 3. ROC curves for proteins of interest in previously undiagnosed ccRCC patients.

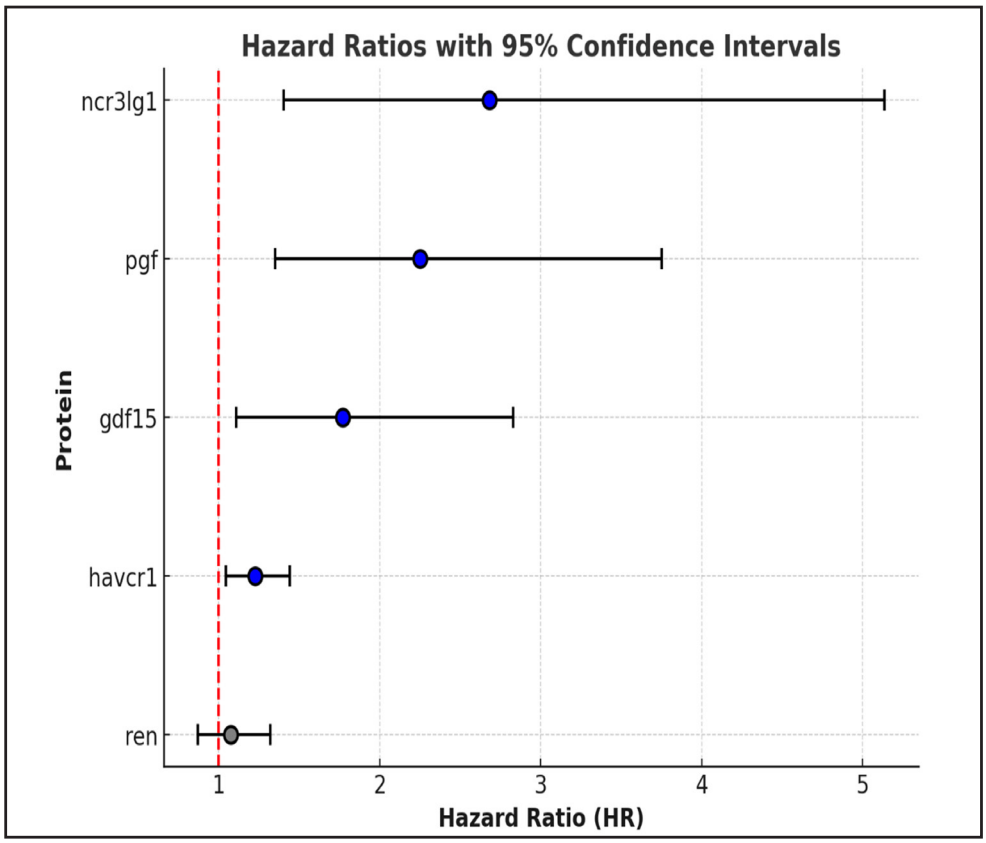

Figure 4. Prognostic Hazard ratios for proteins of interest in all patients diagnosed with ccRCC.

10% missing data were flagged for review, and if the missing data were considered random, single imputation methods (such as median imputation) were applied for proteins deemed essential to the study. We also conducted outlier detection on proteomic data by generating boxplots and calculating z-scores (greater than ±4 standard deviations). Outliers were either excluded or adjusted (Winsorized) when technical errors or assay noise were suspected. Inconsistent or implausible BMI values were reviewed, and any unusual date entries were reexamined and standardized.

To ensure data consistency, Python (version 3.9) was utilized for data merging, outlier detection, and normalization. We employed Pandas, Numpy, Scipy, and Scikit-Learn libraries for data processing and statistical checks. The Tidyverse package in R (version 4.1.2) was used for additional quality control, including verifying missing data patterns and examining distributions of variables.

Statistical Analysis:

We employed time-to-event analyses using Cox proportional hazards regression to investigate the relationship between baseline proteomic profiles and ccRCC risk, as well as overall survival. Of the 127 ccRCC cases identified, 34 were classified as prevalent and 93 as incident, allowing us to study both disease onset and outcomes. Proteins were treated as key explanatory variables, with raw NPX values and standardized z-scores used to model hazard ratios (HRs). These analyses were adjusted for age, sex, BMI, smoking status, and eGFR.

To address multiple comparisons, we applied false discovery rate (FDR) corrections or effective number of tests to adjust for the correlation between proteins. Proteins with FDR-adjusted p-values less than 0.05 were considered significant. To visualize survival data and cumulative incidence of ccRCC diagnoses, Kaplan-Meier curves were generated. We also categorized participants by high or low protein levels (based on median NPX concentration) and performed log-rank tests to compare risk across these groups. In cases where we suspected a dose-response relationship, we further divided the groups into quartiles or tertiles to assess whether risk increased with higher protein levels.

To minimize reverse causation bias, we conducted sensitivity analyses by excluding individuals who developed ccRCC or died within two to three years of baseline. We also stratified analyses by eGFR (<60 vs. ≥60 mL/min/1.73 m^2) and sex to investigate whether associations varied by kidney function or demographic factors.

Reproducibility & Ethical Approvals

The computing environment was documented, including versions of

R (v4.1.2) and Python (3.9), to ensure that the analysis could be replicated. Internal consistency checks were performed to ensure data integrity before final analysis. UKBB participants provided written informed consent, and data were fully de-identified to maintain confidentiality. Ethical approval was granted by the North West Multi-centre Research Ethics Committee, and all procedures adhered to the principles outlined in the Declaration of Helsinki. Although UKBB data cannot be shared publicly due to confidentiality agreements, annotated R scripts, Jupyter notebooks, and data dictionaries are available upon request. Other researchers with approved access to the UKBB can replicate or extend the analysis by using the same methods and scripts. The analysis pipeline can be adapted for other proteomic or omics datasets with similar data structures, such as participant-level CSV files and log-transformed continuous markers.

RESULTS

503,317 adults aged 39–73 years were analyzed utilizing the UK Biobank. Of these 347,576 met eligibility criteria, Olink PEA was performed on 49,217 of these participants. We then identified our cohorts as defined above with 34, 93 and 49,090 patients in Group 1, 2 and 3 respectively.

Predictive serum biomarkers for ccRCC

Our findings revealed the strongest predictive associations between elevated levels of HAVCR1, REN, INHBB, NCR3LG1, and previously undiagnosed ccRCC (Group 2), with these proteins showing increased HR for cancer association (95% CI) (Figure 2). Among these, HAVCR1 was most pronounced (HR 5.1, 95% CI: 3.6-7.3, p<0.001) underscoring its potential as a powerful diagnostic indicator in ccRCC screening. REN, INHBB, NCR3LG1, and PGF all exhibited strong performance as well, showing HR 1.5 95% CI: 1.1-2.2, p<0.02; HR 1.8 95% CI: 0.9-3.5, p<0.09; HR 3.7 95% CI: 1.7-8.1, p<0.001; HR 3.9 95% CI: 1.2-13.1, p<0.03; respectively. Operating characteristic curve analysis demonstrated strong predictive capabilities for each protein of interest as follows: HACVR1 (AUC 0.8756; SN 0.8108; SP 0.7798), REN (AUC 0.6777; SN 0.5135; SP 0.7720), INHBB (AUC 0.7189; SN 0.4865; SP 0.8530), NCR3LG1 (AUC 0.6935; SN 0.1892; SP 0.9325), and PGF (AUC 0.8216; SN 0.2703; SP 0.9475). These biomarkers, individually and collectively, exhibited high sensitivity and specificity for ccRCC detection (Figure 3).

Prognostic serum biomarkers for ccRCC

In all patients previously diagnosed with ccRCC (Groups 1 and 2 combined), we examined protein-to-cancer associations as potential indicators of prognosis, or overall survival. Note that the hazard ratios in the previous analysis for Group 2 specifically reflect the likelihood of developing ccRCC, whereas in this analysis, the hazard ratios pertain to overall survival in diagnosed pa-

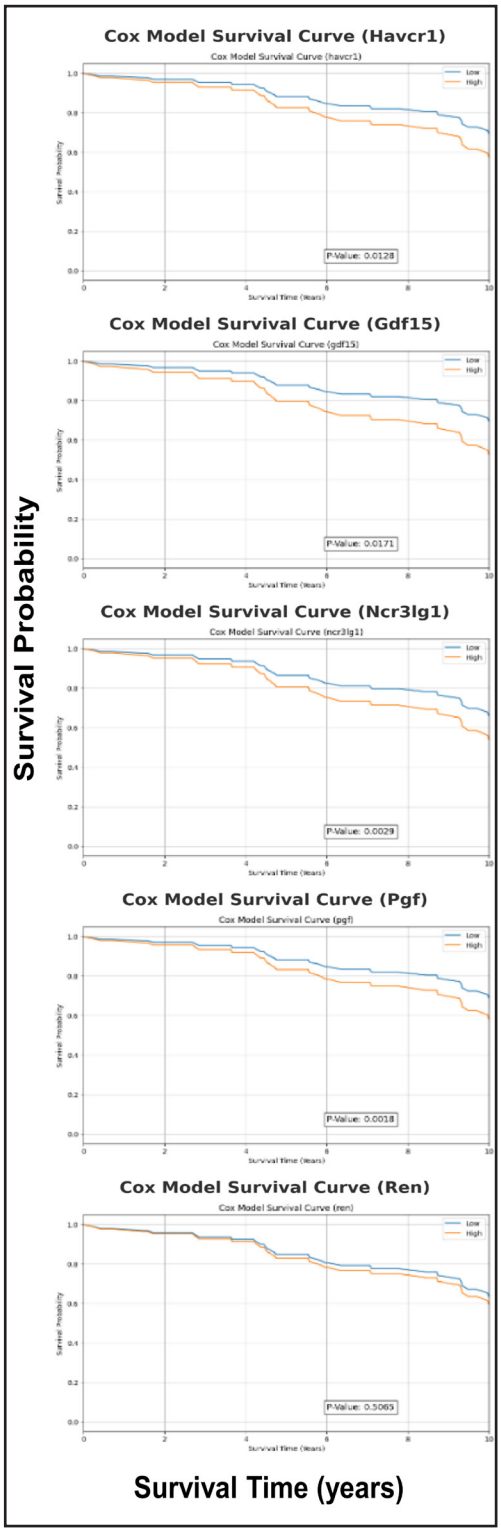

Figure 5. Cox Survival Curves for proteins of interest in all patients diagnosed with ccRCC.

tients. Among the identified biomarkers, NCR3LG1 demonstrated the strongest prognostic association with survival in ccRCC, exhibiting the highest hazard ratio (HR 2.6, 95% CI: 1.4–5.1, p<0.002). This was followed by PGF (HR 2.2, 95% CI: 1.3–3.8, p<0.001) and GDF15 (HR 1.8, 95% CI: 1.1–2.8, p<0.02). HAVCR (HR 1.2, 95% CI: 1.0–1.4, p<0.01) and REN (HR 1.1, 95% CI: 0.8–1.3, p=0.5) also emerged as notable candidates, though with comparatively lower effect sizes. (Figure 4).

Cox regression curves were generated for the proteins identified above separated by high vs. low serum protein concentration. Higher concentrations of all proteins, except REN, were significantly associated with decreased survival probability. (Figure 5).

Kaplan-Meier analysis was performed for proteins of interest in this group, stratified by high versus low protein concentration, while adjusting for GFR. Over the 10-year follow-up, all proteins exhibited a trend toward decreased survival. However, only PGF demonstrated a statistically significant association with reduced survival (p<0.006). HAVCR1 (p=0.07), GDF15 (p=0.1), and NCR3LG1 (p=0.2) followed a similar trend but did not reach statistical significance. REN remained the only protein showing no survival difference based on concentration (p=0.6). (Supplementary Figure 1).

DISCUSSION

Our study found significant association with elevations of HAVCR1, REN, INHBB, NCR3LG1, and PGF and previously undiagnosed ccRCC, indicating their potential as diagnostic markers. In particular, HAVCR1 was identified as a potential predictive biomarker for ccRCC, with a hazard ratio of 5.1. NCR3LG1, PGF, HAVCR1, and GDF15 were also associated with decreased survival in patients with diagnosed ccRCC.

In addition to examining protein-cancer risk associations, we also assessed the predictive capability of high performing protein markers in Group 2, or patients who later developed ccRCC, using AUC metrics. This analysis confirmed HAVCR1 as a top performer, demonstrating the highest predictive power (AUC 0.8756; SN 0.8108; SP 0.7798). By demonstrating the highest sensitivity among all other protein biomarkers, HAVCR1 has the potential as a marker for early detection of ccRCC. By contrast, NCR3LG1 (SP 0.9325) and PG (SP 0.9475) exhibited the strongest specificities in our cohort, identifying them as ideal candidates for confirmation of ccRCC in patients suspected to have the disease.

In our group of all ccRCC patients, NCR3LG1 showed the greatest promise as a prognostic marker with a hazard ratio of 2.6, and decreasing survival probability with increasing protein concentration. Kaplan-Meier analysis showed that PGF exhibited a statistically significant decrease in survival (p<0.006) with higher protein concentrations, highlighting its potential as a prognostic marker in disease surveillance for ccRCC patients. Other proteins, including HAVCR1, GDF15, and NCR3LG1, showed trends toward decreased survival, but none reached statistical significance. This suggests that while these proteins might indicate a negative prognosis, further investigation is required to confirm their role in treatment outcomes.

The biological functions of these proteins solidify their potential use in diagnosis and prognosis of ccRCC, as several of these proteins have already been implicated in RCC carcinogenesis. HAVCR1 (Hepatitis A Virus Cellular Receptor 1), alternatively known as KIM-1 (Kidney Injury Molecule 1), is a transmembrane receptor that is induced in response to kidney injury. It activates the IL-6/STAT-3 pathway, known to drive tumorigenesis by stimulating proliferation, immune evasion, and metastasis. Overexpression of HAVCR1 has been linked to greater tumor aggressiveness in RCC, supporting its potential as a prognostic marker[5,6]. Previous studies show that increased HAVCR1 expression correlates with higher IL-6 levels, a known marker for renal malignancy.[7,8] Additionally, studies have suggested that elevated HAVCR1/KIM-1 pre-nephrectomy is associated with worse outcomes, such as metastasis-free survival (MFS) and overall survival (OS) and that higher HAVCR1/KIM-1 levels after treatment with nivolumab and

ipilimumab correlated with lower OS[9,10]. These findings are consistent with our own, which show strong associations with elevated HAVCR1 with development of ccRCC, and the risk of decreased survival. However, contradictory findings by Lee *et al.* suggest a possible positive prognostic role for HAVCR1 in some cases[11].

NCR3LG1 (Natural Cytotoxicity Triggering Receptor 3 Ligand 1), a ligand for NKp30 on natural killer cells, has been linked to immune evasion in RCC. Altered NCR3 splice variants contribute to deficient NK cell function, enabling tumor cells to evade immune surveillance.[12] PGF (Placental Growth Factor), a member of the VEGF family, plays a key role in angiogenesis. Elevated PGF levels are associated with higher RCC tumor grades and increased vascularity, making it a promising prognostic marker and therapeutic target[13].

Similarly, GDF15 (Growth Differentiation Factor 15), a member of the TGFβ family, is implicated in carcinogenesis, promoting tumor progression and treatment resistance in various cancers[14–16]. However, a recent study by Yang *et al.* found decreased GDF15 in ccRCC, challenging its role as a prognostic factor.[17] In contrast, GDF15 elevation in our analysis was linked to poor prognosis, suggesting a complex role in RCC progression.

REN (Renin), typically involved in blood pressure regulation, may influence RCC indirectly through the renin-angiotensin system (RAS). In fact, a study by Nuzzo et al. found that combining RAS inhibitors with immune checkpoint inhibitors improved OS in metastatic RCC patients, suggesting a potential therapeutic role for REN in RCC management[18].

Our findings highlight the potential of HAVCR1, PGF, NCR3LG1, and REN as emerging biomarkers for both the early detection and prognosis of ccRCC in line with many previous studies mentioned above. HAVCR1, in particular, demonstrated the strongest predictive power, with high sensitivity for early detection and strong associations with ccRCC. PGF and NCR3LG1 exhibited strong prognostic potential, making them ideal candidates for confirming ccRCC diagnoses or progression in suspected patients or guiding risk based treatment strategies. These proteins, especially when considered together in a multi-biomarker panel, may offer more robust diagnostic and prognostic capabilities than relying on individual markers alone. While further research is needed to validate these findings in larger cohorts, these biomarkers offer promise for improving ccRCC diagnosis, patient stratification, and monitoring of disease outcomes.

LIMITATIONS

Our study's findings may not be generalizable to non-European populations due to the UKBB's demographic composition. Additionally, treatment information following diagnosis of ccRCC was also limited which in turn limited the granularity of the study. Finally, while we adjusted for common covariates, residual confounding factors, such as other medical conditions could still affect the results. Future studies with larger sample sizes and longer follow-up are needed to confirm the clinical utility of these biomarkers.

FUTURE DIRECTIONS

Future research could expand the proteomic panel and integrate complementary modalities, such as genomics and radiomics, to refine RCC risk prediction models. These biomarkers could eventually be incorporated into multi-institutional studies and risk prediction tools for targeted screening. However, validation in independent cohorts will be crucial before clinical implementation.

CONCLUSION

Our study identifies several promising serum biomarkers—HAVCR1, PGF, and NCR3LG1—associated with both early detection and prognosis of ccRCC. Notably, HAVCR1 exhibits strong potential for early detection, while PGF and NCR3LG1 demonstrate significant prognostic value in diagnosed patients. Further validation in larger cohorts is necessary to confirm these findings and evaluate their clinical utility across diverse populations.

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