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Area Deprivation and Risk of Death and CKD Progression: Long-Term Cohort Study in Patients under Unrestricted Nephrology Care

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Keywords
Deprivation · Chronic kidney disease

Abstract
Background: Area deprivation index (ADI) associates with prognosis in non-dialysis CKD. However, no study has evaluated this association in CKD patients under unrestricted nephrology care. ***Methods:*** We performed a long-term prospective study to assess the role of deprivation in CKD progression and mortality in stage 1–4 CKD patients under regular nephrology care, living in Naples (Italy). We used ADI calculated at census block levels, standardized to mean values of whole population in Naples, and linked to patients by georeference method. After 12 months of "goal-oriented" nephrology treatment, we compared the risk of death or composite renal outcomes (end-stage kidney disease or doubling of serum creatinine) in the tertiles of standardized ADI. Estimated glomerular filtration rate (eGFR) decline was evaluated by mixed effects model for repeated eGFR measurements. ***Results:*** We enrolled 715 consecutive patients (age: 64 ± 15 years; 59.1% males; eGFR: 49 ± 22 mL/min/1.73 m^2). Most (75.2%) were at the lowest national ADI quintile. At referral, demographic, clinical, and therapeutic features were similar across ADI tertiles; after 12 months, treatment intensification allowed better control of hypertension, proteinuria, hypercholesterolaemia, and anaemia with no difference across ADI tertiles. During the subsequent long-term follow-up (10.5 years [interquartile range 8.2–12.6]), 166 renal events and 249 deaths were registered. ADI independently associated with all-cause death (p for trend = 0.020) and non-cardiovascular (CV) mortality (p for trend = 0.045), while CV mortality did not differ (p for trend = 0.252). Risk of composite renal outcomes was similar across ADI tertiles (p for trend = 0.467). The same held true for eGFR decline (p for trend = 0.675). ***Conclusions:*** In CKD patients under regular nephrology care, ADI is not associated with CKD progression, while it is associated with all-cause death due to an excess of non-CV mortality.

Introduction

In CKD, poor socio-economic status, including low annual household income, poor educational attainment, and neighbourhood deprivation, is associated with higher mortality and faster progression to end-stage kidney

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disease (ESKD) [1–14]. The greater cardiorenal risk in the disadvantaged people might be due to the clustering of comorbidities, unhealthy behaviours, and greater environmental exposures to toxins [15, 16].

Most data on this issue derive from community studies [1, 2, 5–8, 10–14], whereas CKD prognosis by socio-economic status has not been studied in patients referred to the nephrology setting. Indeed, a single cross-sectional study in 1,657 patients referred to the Sheffield Kidney Institute reported a direct relationship between ADI and severity of CKD at presentation [17]. The same study group provided evidence in a retrospective study in 917 CKD patients that a poorest area deprivation index (ADI) was associated with heavy proteinuria and faster CKD progression during the first 3 years of follow-up [18]. However, the analysis of impact of ADI on hard outcomes was precluded because few patients started renal replacement therapy or died during the short follow-up. On the other hand, whether nephrology management may attenuate the detrimental effect of deprivation on the prognosis of CKD patients remains similarly unexplored. Finally, the majority of studies assessing the role of ADI in the onset of CKD have been performed in the USA, where the substantial inequality might be related to the limited access to healthcare [11, 12, 15, 19, 20].

Obtaining data on association between deprivation status and adverse outcome in nephrology setting is essential to correctly plan public health initiative and gain novel insights into the possible role of nephrology referral in CKD prognosis, considering that prognosis of CKD patients may be modified by nephrology management [21–26]. We therefore performed an analysis to assess the risk of CKD progression and mortality associated with ADI in a cohort of consecutive CKD patients under regular nephrology care in Italy, a country where access to tertiary care is unrestricted and granted by the National Health System [27, 28].

Methods

Study Design and Selection Criteria

This is a cohort study carried out in adult CKD patients, no dialysis/no kidney transplant, referred and regularly followed in outpatient nephrology clinic of University of Campania "Luigi Vanvitelli" of Naples (Italy), living in the municipality of Naples. We selected consecutive patients referred from January 2001 to December 2010 with CKD stages 1–4 and with at least 12 months of nephrology treatment. Patients with active malignancy, severe cirrhosis, heart failure, and evidence of acute kidney injury in the 3 months prior to the referral visit were excluded.

Data Collection

For this analysis, we considered variables collected at the first nephrology visit ("referral visit") and after 1 year of nephrology follow-up ("12-month visit"). At referral visit, we collected demographics, medical history, office blood pressure (BP), laboratory and instrumental findings, and therapy. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation; the creatinine measurement was not standardized to isotope dilution mass spectrometry, so that the creatinine concentrations were reduced by 5% (the established calibration factor) [29].

Exposure: ADI

We used ADI derived by socio-economic attributes available for the Italian population who took part in the 2001 Census, including information about education level, employment, home ownership, single-parent family, and overcrowding. ADI has been already used in epidemiological research to measure social and material deprivation at census block level [27]. We recalculated ADI by summing up the *z*-scores of 5 simple indicators, considering mean values and SD in the municipality of Naples (Italy), accounting for 1,004,577 people and 4,033 blocks (Census 2001). Patients were georeferenced using Google Maps service and linked to ADIs. The linkage was made with the patients' address collected at the referral visit. We checked the maintenance of address at the end of follow-up, by consulting the patients' charts and/or regional registries when patients died.

Treatment Goals

All participating nephrologists shared the following main goals for treatment: BP values ≤130/80 mm Hg in CKD patients with abnormal proteinuria (>0.15 g/24 h) and/or diabetes, BP values ≤140/90 mm Hg in patients without proteinuria and/or diabetes, haemoglobin (Hb) level ≥11 g/dL, and proteinuria ≤0.15 g/24 h. Cholesterol was defined at target if serum levels were <190 mg/dL. Serum phosphate level was considered at target if <4.6 mg/dL. The prevalence of achievement of the above targets was evaluated at referral and at 12-month visit.

Outcomes and Follow-up

Primary end points were time to composite renal outcomes, defined as serum creatinine doubling or chronic dialysis initiation or kidney transplantation (ESKD), whichever occurred first, and time to all-cause mortality before ESKD. Survival analysis lasted from 12-month visit to December 31, 2018, death, ESKD, or preemptive kidney transplantation and censored on the date of the last nephrology clinic visit. If the patient missed a scheduled visit, he/she was recalled by nephrologists to plan the following visit. If missing visit was due to an event (ESKD or death), this was verified and confirmed by means of either regional dialysis registry (date of ESKD) or death certificates provided by Mortality Registry Office (date and cause of death). The occurrence of doubling creatinine was confirmed at the following visit occurring within 60 days. We performed a secondary survival analysis about cause-specific deaths by separating all-cause deaths in cardiovascular (CV) and non-CV (neoplastic and non-neoplastic) deaths.

Statistical Analysis

Continuous variables were reported as either mean ± SD or median and interquartile ranges (IQR) according to their distribu-

tion. Patient ADI value was categorized by tertile categories. Intra-group differences from referral visit to 12-month visit were analysed using paired Student's *t* test or the Wilcoxon test, while inter-group differences were tested by either 1-way ANOVA or the Kruskal-Wallis test. Categorical variables were reported as percentages and analysed by the McNemar test (intra-group differences) or χ^2 test (inter-group differences).

Median follow-up was estimated by the inverse Kaplan-Meier approach. Incidence rates of end points were computed from the number of events divided by the person-time and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. To assess the role of ADI (in tertiles) in the risk of ESKD and all-cause death, we used multivariable Cox proportional hazards models and computed the event-specific hazard ratio (HR) and 95% CI. We performed 4 models for each outcome with progressive adjustment for the following variables (measured at 12-month visit): model 1, adjusted for age, gender, and eGFR; model 2, including model 1 plus diabetes, BMI, previous cardiovascular disease (CVD), smoking, and LVH; model 3, including model 2 plus systolic BP, log-transformed proteinuria, Hb, serum phosphate, and use of renin-angiotensin system (RAS) inhibitors. Finally, we built a survival model (model 4), including model 2 plus proportion of treatment success for BP, Hb, proteinuria, phosphate, cholesterol, and use of RAS inhibitors. Correlation between ADI and continuous variables was tested by multiple regression analysis.

A sensitivity analysis was performed to test the association between continuous ADI values and outcomes by means of restricted cubic spline with 3 knots located at specific quintiles of the continuous ADI (0.10, 0.50, and 0.90). To estimate the variation in eGFR during follow-up, we used a mixed-effects regression model; this method utilizes all available eGFR measurements over follow-up and can properly account for correlation between repeated measures. Mixed-effects regression model included patients with at least 1 eGFR measurement after 12-month visit and added a penalty for initiation of dialysis by imputing an eGFR of 5 mL/min per 1.73 m^2 at the day of dialysis start [30]. Model was adjusted for the same covariates used in the Cox models; time measurement, ADI, and their interaction were included in the mixed model as covariates. A 2-tailed p value <0.05 was considered as significant. Data were analysed by using STATA version 14 (College Station, TX, USA) and R version 3.5 (R Foundation for Statistical Computing, Vienna, Austria).

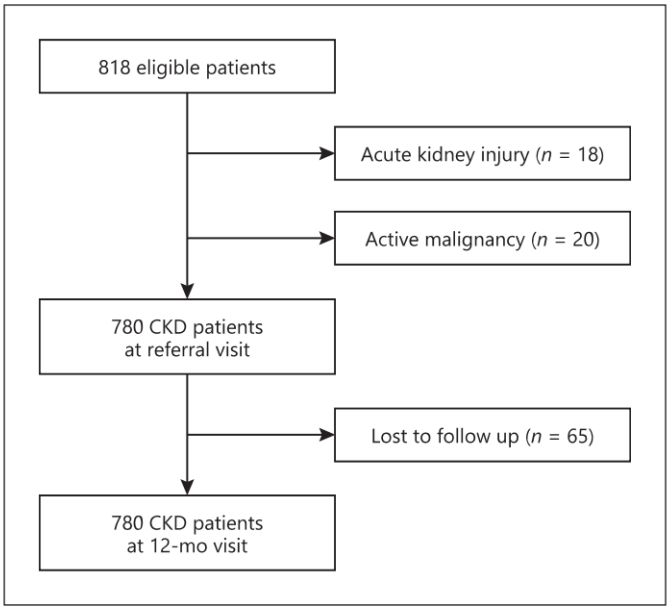

Fig. 1. Flow diagram of the study. No patient was excluded for cirrhosis or heart failure.

Results

Referral Visit

We studied 715 CKD patients out of 818 eligible CKD patients living in the municipality of Naples (Italy). As illustrated in the flow chart (Fig. 1), 65 patients were excluded from analysis, because they were lost after referral visit and no data were available about their follow-up.

With respect to national ADI levels, study cohort was characterized by high level of deprivation as testified by 75.2% patients classified in the 5th national ADI quintile, 13.2% in the 4th ADI quintile, and the remaining 11.6% in the first, second, and third ADI quintiles. Median value of ADI recalculated according to the mean values of city of Naples was 0.01 (IQR: −1.87 to 2.68). The values of the first and third ADI tertiles were −1.12 (IQR: −1.38, −0.84) and 1.65 (IQR: 1.30, 2.09), respectively.

At referral visit, whole cohort was characterized by advanced age, high prevalence of diabetes, previous CVD, and hypertensive nephropathy. The distribution of patients by CKD stage was as follows: 23% in stage 1–2, 29% in stage 3a, 30% in stage 3b, and 18% in stage 4. No difference in demographic, clinical, and therapeutic features was evident throughout ADI tertile categories with exception of high Hb values detected in the low ADI category (Tables 1, 2 and 3).

First Year of Nephrology Care

In the first 12 months of nephrology care, eGFR did not change overall as across ADI tertiles (Table 2). During this period, we observed a substantial reduction in BP and total cholesterol as well as a slight improvement in proteinuria and Hb (Table 2). These changes translated into a significant improvement at 12-month visit in the prevalence of therapeutic goal of BP (from 36.4 to 44.5%), proteinuria (from 41.5 to 49.5%), Hb (from 82.8 to 88.0%), and cholesterol (from 51.2 to 64.9%). A better control of these risk factors was consistently detected in each ADI tertile (Fig. 2) and associated with an increment of the prescription of anti-hypertensive drugs, RAS inhibitors,

Table 1. Demographic and clinical features of cohort stratified by ADI tertiles

	Overall	ADI T1	ADI T2	ADI T3	*p* value
Number	715	238	239	238	
Age, years	64.3±14.8	64.0±14.9	63.9±15.8	65.0±13.6	0.68[a]
Males, %	58.9	64.3	56.9	55.5	0.11[b]
Diabetes, %	35.4	38.3	33.5	34.5	0.52[b]
CVD, %	43.6	42.4	42.3	46.2	0.62[b]
BMI, kg/m^2	29.0±5.3	28.9±5.2	28.9±5.1	29.2±5.6	0.79[a]
CKD diagnosis					
Hypertensive	54.5	52.1	53.1	58.8	
Diabetic	16.2	18.5	15.1	15.1	
Glomerular	16.4	17.7	18.4	13.0	0.58[b]
TIN	9.4	9.7	9.6	8.8	
ADPKD	3.4	2.1	3.8	4.2	
ADI components[c]					
% of less educated people	36.4±13.0	24.5±9.2	36.5±6.8	48.2±9.6	–
% of unemployed people	30.4±14.7	17.7±7.0	29.2±8.5	44.5±12.8	–
% of home for rent	42.6±22.0	26.3±14.2	39.6±14.8	62.1±19.2	–
% of single-parent families	11.6±5.6	10.8±4.3	11.0±3.4	13.1±7.7	–
Household crowding index	4.0±1.0	3.1±0.6	3.9±0.6	4.9±0.9	–

Continuous data are reported as mean±SD. ADI, area deprivation index; CVD, cardiovascular disease; ADPKD, autosomal dominant polycystic kidney disease; TIN, tubule-interstitial nephropathy. [a] *p* values are referred to one-way ANOVA. [b] χ^2 test. [c]Mean±SD of values calculated at Census block level for each patient.

statin, and erythropoiesis-stimulating agents (Table 3). No association was found between ADI and the major modifiable risk factors (BP, proteinuria, serum phosphate, and Hb).

Survival Analysis

During a median follow-up of 10.5 years (IQR 8.2–12.8), we registered 166 renal events corresponding to an incidence rate of 3.0/100 patient-year (95% CI: 2.0–3.5). No significant difference in incidence rate of renal events was found across ADI tertiles, and this holds true also for the distinct components of the combined renal event. Indeed, we found 107 dialysis events, corresponding to incidence of 1.8/100 patient-year (95% CI: 1.5–2.2), similar across ADI tertile categories (see online suppl. Table 1; see www.karger.com/doi/10.1159/000509351 for all online suppl. material). Cox analysis demonstrated that ADI was not associated with renal outcome after multiple adjustments for the main modifiable and unmodifiable risk factors for CKD progression and after adjustment for prevalence of treatment goals (Table 4).

Similar data were attained when examining the eGFR decline (median: 8 measurements/patient, IQR: 5–12). Mixed effects regression showed a similar eGFR decline across ADI tertiles (interaction time × ADI $p = 0.68$): unadjusted eGFR change (mL/min/1.73 m^2/year) from highest to lowest ADI tertile was −1.42 (95% CI: −1.67, −1.17), −1.31 (95% CI: −1.57, −1.04), and −1.47 (95% CI: −1.74, −1.20). Similar results were obtained in the adjusted model with an interaction time × ADI $p = 0.67$.

We found 259 all-cause deaths (4.4/100 patient-year, 95% CI: 3.9–5.0). Death had a CV cause in 52.9% of cases, neoplasia in 22.0%, other causes in 16.2%, and unknown in 8.9%. Incidence rate of all-cause mortality was 3.6/100 patient-year (95% CI: 2.9–4.5) in lowest ADI tertile category and 4.9/100 patient-year (95% CI: 4.0–6.0) in both highest and intermediate ADI categories (online suppl. Table 1). Multivariable Cox proportional hazards models for all-cause mortality are reported in Table 4. We found that highest level of deprivation was associated with an increased mortality risk after adjustment for age, gender, and eGFR (model 1). This result persisted after adjustments for the main unmodifiable (model 2) and modifiable risk factors (model 3). Same results were obtained when continuous variables were replaced by prevalence of treatment success at 12-month visit (model 4). Results of full Cox models are reported in online suppl. Tables 1 and 2. Sensitivity analysis testing the association of continuous ADI value with outcomes adjusted for the covariates included in model 3 showed a significant association

Table 2. Clinical and laboratory parameters at referral and 12-month visit in patients stratified by ADI tertiles

	Overall	ADI T1	ADI T2	ADI T3	*p* value
eGFR, mL/min/1.73 m^2					
Referral visit	49.6±22.4	51.0±22.6	49.7±22.8	47.9±21.8	0.32[a]
12-month visit	48.9±22.8	50.3±22.9	49.8±23.3	46.5±22.3	0.13[a]
p value[b]	0.133	0.417	0.951	0.070	
Systolic BP, mm Hg					
Referral visit	142±23	141±23	143±22	142±23	0.68[a]
12-month visit	135±19	135±19	135±19	137±19	0.22[a]
p value[b]	<0.0001	<0.0001	<0.0001	0.0011	
Diastolic BP, mm Hg					
Referral visit	81±12	80±11	81±13	81±12	0.51[a]
12-month visit	77±12	77±11	77±12	77±12	0.78[a]
p value[b]	<0.0001	0.0002	<0.0001	<0.0001	
Proteinuria, mg/24 h					
Referral visit	0.18 (0.08–0.75)	0.18 (0.07–0.84)	0.18 (0.07–0.80)	0.18 (0.08–0.60)	0.72[c]
12-month visit	0.18 (0.05–0.60)	0.18 (0.04–0.56)	0.17 (0.05–0.68)	0.19 (0.05–0.60)	0.97[c]
p value[d]	0.0001	0.0134	0.113	0.0096	
Cholesterol, mg/dL					
Referral visit	195±50	197±50	193±46	194±54	0.44[a]
12-month visit	182±39	182±39	183±42	179±37	0.43
p value[b]	<0.0001	<0.0001	0.002	0.0001	
Haemoglobin, g/dL					
Referral visit	13.0±2.0	13.2±2.0	12.9±2.0	12.7±1.9	0.006[a]
12-month visit	13.0±1.7	13.2±1.7	13.1±1.7	12.8±1.7	0.04[a]
p value[b]	0.158	0.667	0.268	0.086	
Calcium, mg/dL					
Referral visit	9.4±0.7	9.4±0.6	9.4±0.7	9.4±0.7	0.65[a]
12-month visit	9.4±0.6	9.4±0.6	9.4±0.7	9.3±0.7	0.32[a]
p value[b]	0.507	0.188	0.430	0.458	
Phosphate, mg/dL					
Referral visit	3.8±0.8	3.7±0.7	3.8±0.8	3.8±0.8	0.08[a]
12-month visit	3.7±0.8	3.7±0.7	3.8±0.7	3.8±0.8	0.17[a]
p value[b]	0.423	0.978	0.847	0.278	
PTH, pg/mL					
Referral visit	68 (41–98)	67 (41–100)	70 (46–95)	68 (38–101)	0.69[c]
12-month visit	66 (40–106)	62 (40–97)	70 (41–106)	66 (39–112)	0.66[c]
p value[d]	0.989	0.577	0.943	0.654	

Data are reported as mean ± SD or median and interquartile ranges, according to their distribution. ADI, area deprivation index; eGFR, estimated glomerular filtration rate; BP, blood pressure. [a] *p* values are referred to 1-way ANOVA. [b] Paired *t* test. [c] Kruskal-Wallis test. [d] Wilcoxon test.

with all-cause death ($p = 0.046$, online suppl. Fig. 1), while association was not significant with renal event ($p = 0.515$, online suppl. Fig. 2). We carried out a further Cox analysis using as ADI based on national benchmark values. We found that higher ADI (5th ADI quintile) is associated with higher risk of all-cause death, whereas no interaction was found with composite renal end points (online suppl. Table 4).

Additional Cox analysis was performed to discriminate the potential effect on CV ($n = 137$) and non-CV deaths ($n = 122$). This analysis showed that highest ADI category showed an increased mortality, if compared with lowest ADI category, only for non-CV mortality (highest vs. lowest ADI tertiles, HR: 1.57 [95% CI: 1.01–2.44, $p = 0.046$]), while no association was found for CV death ($p = 0.257$). These results persisted after multiple adjustments (Table 4). We also performed a sensitivity analysis to assess the relationship between ADI and mortality due to neoplastic causes. By this latter analysis, a significant increase in incidence rate of neoplastic deaths

Table 3. Therapeutic features at referral and after 12 months in overall cohort and stratified by ADI tertiles

	Overall	ADI T1	ADI T2	ADI T3	*p* value
BP-lowering drugs	1.92±1.12	1.86±1.13	2.00±1.12	1.90±1.11	0.32[a]
At 12 months	2.72±1.40	2.61±1.38	2.85±1.41	2.69±1.40	0.19[a]
p value[b]	<0.0001	<0.0001	<0.0001	<0.0001	
RAS blockers, %	75.4	73.1	77.8	75.2	0.49[c]
At 12 months, %	85.0	82.8	87.5	84.5	0.36[c]
p value[d]	<0.0001	0.0011	0.006	0.0003	
Furosemide, %	23.0	18.5	25.9	23.1	0.14[c]
At 12 months, %	33.4	30.6	34.7	35.7	0.35[c]
p value[d]	<0.0001	<0.0001	0.0008	<0.0001	
ESA, %	3.1	2.1	3.8	3.4	0.55[c]
At 12 months, %	14.0	11.8	13.8	16d	0.35[c]
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001	
Statin, %	29.5	30.3	31.8	26.5	0.42[c]
At 12 months, %	44.1	45.4	46.0	40.8	0.45[c]
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001	
Vitamin D, %	3.8	3.4	3.8	4.2	0.89[c]
At 12 months, %	13.0	13.5	13.0	12.6	0.96[c]
p value[d]	<0.0001	<0.0001	<0.0001	<0.0001	

Data are reported as mean ± SD or percentage. ADI, area deprivation index; BP, blood pressure; RAS, renin-angiotensin system; ESA, erythropoiesis-stimulating agents. [a] One-way ANOVA. [b] Paired *t* test. [c] *p* values are referred to χ^2 test. [d] McNemar's test.

Table 4. Cox analysis of risk of composite renal outcome (serum creatinine doubling or dialysis) and all-cause, CV, and non-CV mortality associated with ADI tertiles

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Renal outcomes								
ADI T2 versus T1	0.94 (0.64–1.39)	0.768	0.91 (0.58–1.28)	0.642	0.85 (0.54–1.20)	0.435	0.95 (0.50–1.15)	0.939
ADI T3 versus T1	1.24 (0.85–1.79)	0.261	1.26 (0.87–1.83)	0.227	1.14 (0.81–1.72)	0.510	1.15 (0.74–1.61)	0.471
p value for trend		0.249		0.216		0.467		0.457
All-cause mortality								
ADI T2 versus T1	1.31 (0.96–1.77)	0.085	1.29 (0.95–1.76)	0.103	1. 31 (0.96–1.79)	0.056	1.31 (0.96–1.78)	0.088
ADI T3 versus T1	1.42 (1.04–1.94)	0.027	1.44 (1.06–1.98)	0.021	1.46 (1.06–1.99)	0.019	1.38 (1.01–1.89)	0.047
p value for trend		0.026		0.021		0.020		0.047
Secondary end points								
CV mortality								
ADI T2 versus T1	1.39 (0.92–2.10)	0.121	1.39 (0.92–2.11)	0.123	1.42 (0.93–2.17)	0.107	1.44 (0.94–2.20)	0.094
ADI T3 versus T1	1.29 (0.83–1.99)	0.257	1.35 (0.87–2.09)	0.187	1.33 (0.86–2.08)	0.205	1.36 (0.87–2.13)	0.174
p value for trend		0.252		0.183		0.206		0.174
Non-CV mortality								
ADI T2 versus T1	1.21 (0.77–1.91)	0.408	1.20 (0.76–1.90)	0.433	1.28 (0.81–2.06)	0.296	1.27 (0.80–2.05)	0.295
ADI T3 versus T1	1.57 (1.01–2.44)	0.046	1.53 (0.99–2.38)	0.063	1.58 (1.01–2.46)	0.045	1.59 (1.02–2.49)	0.043
p value for trend		0.045		0.062		0.044		0.042

ADI, area deprivation index; HR, hazard ratio; model 1, adjusted by age, sex, and eGFR; model 2, model 1 + diabetes, BMI, previous cardiovascular (CV) disease, smoking, and left ventricular hypertrophy; model 3, model 2 + systolic BP, log(proteinuria), haemoglobin, serum phosphate, serum total cholesterol, and renin-angiotensin system blockers use, after the first year of treatment; model 4, model 2 + proportion of treatment success for BP, cholesterol, proteinuria, phosphate, and haemoglobin at 12 months.

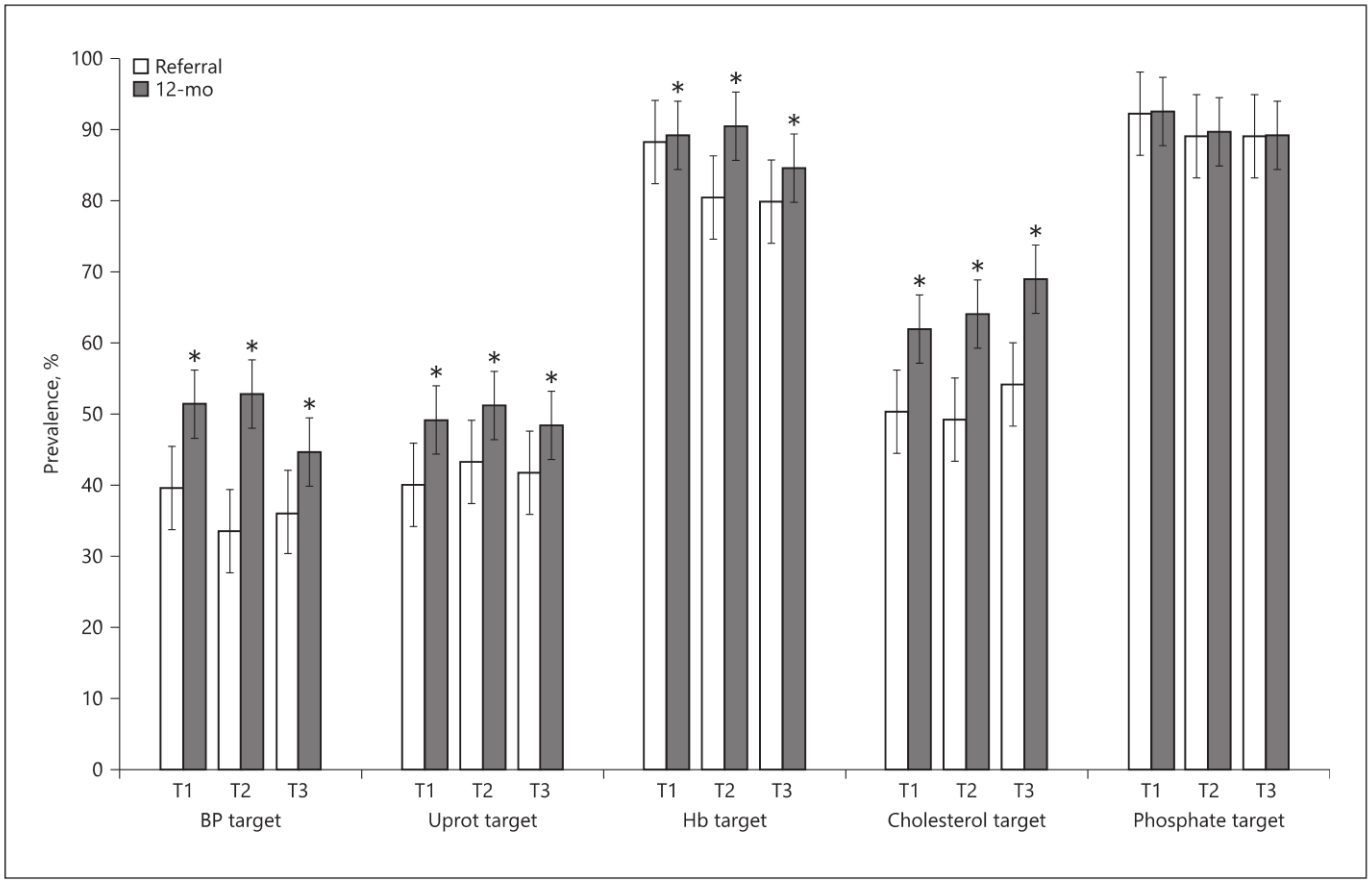

Fig. 2. Prevalence of target for main cardiorenal risk factors at referral (white diagrams) and 12-month (grey diagrams) visits stratified by area deprivation index (ADI) tertiles. T1, 1st ADI tertile; T2, 2nd ADI tertile; T3, 3rd ADI tertile; BP, blood Pressure; Uprot, proteinuria; Hb, haemoglobin.

emerged in most deprived patients ($p = 0.008$; online suppl. Table 1), whereas no difference in non-neoplastic mortality among non-CV causes was found ($p = 0.968$; online suppl. Table 1). The association between highest deprivation and high neoplastic mortality persisted after adjustment for age, gender, and eGFR (highest vs. lowest ADI tertile, HR: 2.77 [95% CI: 1.39–5.51], $p = 0.004$).

Discussion

This long-term prospective study was performed in patients with non-dialysis CKD stage 1–4 and under regular nephrology care for at least 1 year, living in a highly deprived area in Southern Italy. We found that further stratification by tertiles of deprivation level is associated with greater non-CV mortality after adjustment for several risk factors. On the other hand, ADI did not associate with risks of CKD progression and CV mortality. A correct interpretation of our findings needs to consider several issues, including social, economic, and geographic factors, as well as the specific setting of patients.

First, all patients of this cohort lived in the municipality of Naples, embracing a large area of very high population density (1st in Italy, with 8,566 inhabitants per km^2), characterized by high degree of unemployment, low educational status, and poverty [28]. These data are confirmed in our cohort, in which three-quarters of cohort was in 5th quintile of ADI based on national benchmark values. The homogeneous degree of high deprivation in comparison to national level might explain the high prevalence of comorbidities (diabetes, obesity, hypertension, and prior CVD), drawing a similar CV risk profile in the 3 deprivation categories at baseline. A previous study has reported a direct relationship between degree of area de-

privation and severity of CKD at presentation to a UK renal service. In that cohort, however, a larger variability of deprivation scores was recorded [17]. This is the biggest flaw of our study, because we cannot examine the impact of the whole spectrum of ADI; on the other hand, this allowed us to provide novel insights into patients with high level of deprivation.

Our findings confirm that patients with highest levels of deprivation have a higher risk of mortality irrespective of the main known risk factors in CKD patients (online suppl. Table 4). The standardization of ADI based on mean values of municipality of Naples has allowed a further risk stratification of these higher risk patients (Table 4), showing an independent association with all-cause mortality in patients with worst socio-economic conditions (online suppl. Fig. 1). These data are consistent with previous study in general population [1] and CKD cohorts [3].

In disagreement with previous studies, showing a direct correlation between entity of deprivation and renal and CV outcomes [1, 3, 8, 10–14], we did not find any association between ADI and renal end points (Table 4; online suppl. Fig. 2). Although the lack of variability of ADI might explain the absence of association with CKD progression, we should keep in consideration some issues. First, at variance with early studies [1, 3, 8, 10–14], all patients enrolled in the study were referred and followed in our structured renal clinic. Noteworthy, the free universal care for our patients allows to exclude the confounding effect of limited access to tertiary care in disadvantaged patients evidenced in previous studies [31–33]. During the first year of nephrology care, the treatment intensification was implemented by a similar extent in all patients, improving the main CKD and CV risk factors, independently from their deprivation status (Table 3). Interestingly, the effect on the renal end points was confirmed when examining the eGFR decline by mixed model based on a large number of eGFR tests collected for a long period. This is an additional major point of originality because early studies on this issue only evaluated CKD progression as ESKD onset [3, 5, 10–14] or delta eGFR on only 2 time points [1, 18]. Of note, moreover, the only previous study reporting occurrence of ESKD among CKD patients referred in renal clinic was flawed by the low number of renal events ($n = 37$) that did not allow a reliable estimate of deprivation effects on ESKD risk [18]. In addition, we found the lack of association between CV mortality and ADI level (Table 4).

All these results might be the consequence of the beneficial effects on CV cardiorenal risk attained in renal clinics mediated by lowering of BP and proteinuria, correction of anaemia, and increased use of agents counteracting angiotensin II activity [34, 35]. However, the observational design of our study cannot demonstrate any cause-effect relationship. Of note, moreover, the lack of association between ADI and modifiable factors may exclude the possible mediation role of nephrological intervention in the outcomes. Further studies with larger sample size are definitely needed to allow a mediation analysis on this association adequately powered.

We found an increase of mortality in most deprived patients due to non-CV causes (online suppl. Table 1), as already reported in other cohorts [36, 37]. In particular, we showed an increased risk of neoplastic mortality in higher deprived patients. It is therefore reasonable to suggest a role for potential environmental exposure to toxic agents and/or lifestyle behaviours (e.g., poor diet and alcoholism) in patient who are most deprived, as reported in general population [15, 16].

This study has limitations. First, we cannot explore the interaction between area deprivation and ethnic groups other than Caucasian, although this association has been similarly reported by some investigators in blacks and whites [1, 4–6, 11, 25, 26, 32]. Second, the single-centre dimension may limit generalizability of our results; however, this feature also did facilitate concordance of nephrologists on the therapeutic approach. Third, we used ADI based on 2001 census that may change over time; however, cohort's baseline features referred to the same time period (2001–2010). Fourth, we cannot exclude survival bias due to the selection of patients with at least 1 year of nephrology care, although ESKD rate is similar to that reported in referred CKD population with similar eGFR levels at baseline [38, 39]. Finally, individual socio-economic indexes are not available here; this may be a potential limitation of our study (ecological fallacy) [40]. On the other hand, main strengths of the study are the comprehensive data on nephrology care, the prolonged follow-up, and the multiple eGFR measurements.

In conclusion, in a deprived CKD cohort under unrestricted access to nephrology care, higher levels of deprivation are not associated with CKD progression and CV mortality, while being still associated with non-CV death. These findings suggest the major role of unrestricted access to nephrology care to improve cardiorenal prognosis of CKD patients living in highly deprived area.

Although this study has not been designed to evaluate the efficacy of universality of health system on the prognosis of CKD patients, our findings provide additional

insights into the concept that universal access to healthcare improves life expectancy. This has been recently suggested by Global Burden Disease group after comparison of Italian Health Service with other 15 western European countries for more 25 years [41]. Similarly, the latest US national programme of kidney disease prevention (Healthy People 2020) has focused on the elimination of healthcare disparities due to socio-economic levels [42].

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Statement of Ethics

The study was approved by the Institutional Review Board (University of Campania "Luigi Vanvitelli," Naples, Italy) and patients gave written consent to use their clinical data.

Conflict of Interest Statement

All authors declared no sponsorship or funding arrangement related to the study, and no conflict of interest as well.

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Author Contributions

Research idea and study design: S.B., P.C., C.G., N.C., R.M., L.N., and G.C.; data acquisition: S.B., C.G., M.P., T.S., and V.S.; data analysis/interpretation: S.B., C.G., P.C., N.C., V.S., M.A., S.P., N.C., T.S., R.M., L.N., and G.C.; statistical analysis: S.B., M.P., V.S., P.C., and C.G.; and supervision or mentorship: R.M., N.C., S.P., M.A., L.N., and G.C. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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