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Original research

Environmental pollution is associated with poorer survival in patients with adrenocortical carcinoma: findings from a national cohort study in Italy

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Abstract

Background **The impact of environmental pollution on adrenocortical carcinoma (ACC) remains largely unexplored. Although a few studies have assessed the incidence of ACC in polluted areas, no data are available on clinical outcomes.**

Methods **We carried out a retrospective multicentre cohort study in adult patients with ACC diagnosed in 12 referral centres in Italy (1990-2018). We stratified patients for (1) residence in sites officially classified as contaminated (NPCSs [National Priority Contaminated Sites]) or in non-contaminated areas and (2) urbanization, as a contextual proxy for environmental exposure. Outcomes were recurrence-free survival (RFS) and overall survival (OS).**

Results **Among 336 patients, 250 had localized disease (stage I-III) and 86 metastatic disease (stage IV). Subgroups among patients with stage IV ACC were too small for a meaningful analysis. Among patients with localized ACC, 26 (10.4%) living in NPCSs had significantly shorter median RFS (13 vs 43 months; $P = .011$) and OS (67 vs 142 months; $P = .016$) compared to the 224 patients living in non-contaminated areas. At multivariable analysis, residence in NPCSs was independently associated with both recurrence (HR 1.89, 95% CI 1.13-3.16, $P = .016$) and death (HR 2.44, 95% CI 1.39-4.28, $P = .002$). No significant association was found between the level of urbanization and survival.**

Conclusions **This study provides the first evidence that environmental pollution is associated with worse clinical outcomes in patients with ACC. By linking contaminated-area residence with prognosis, these findings raise the possibility that**

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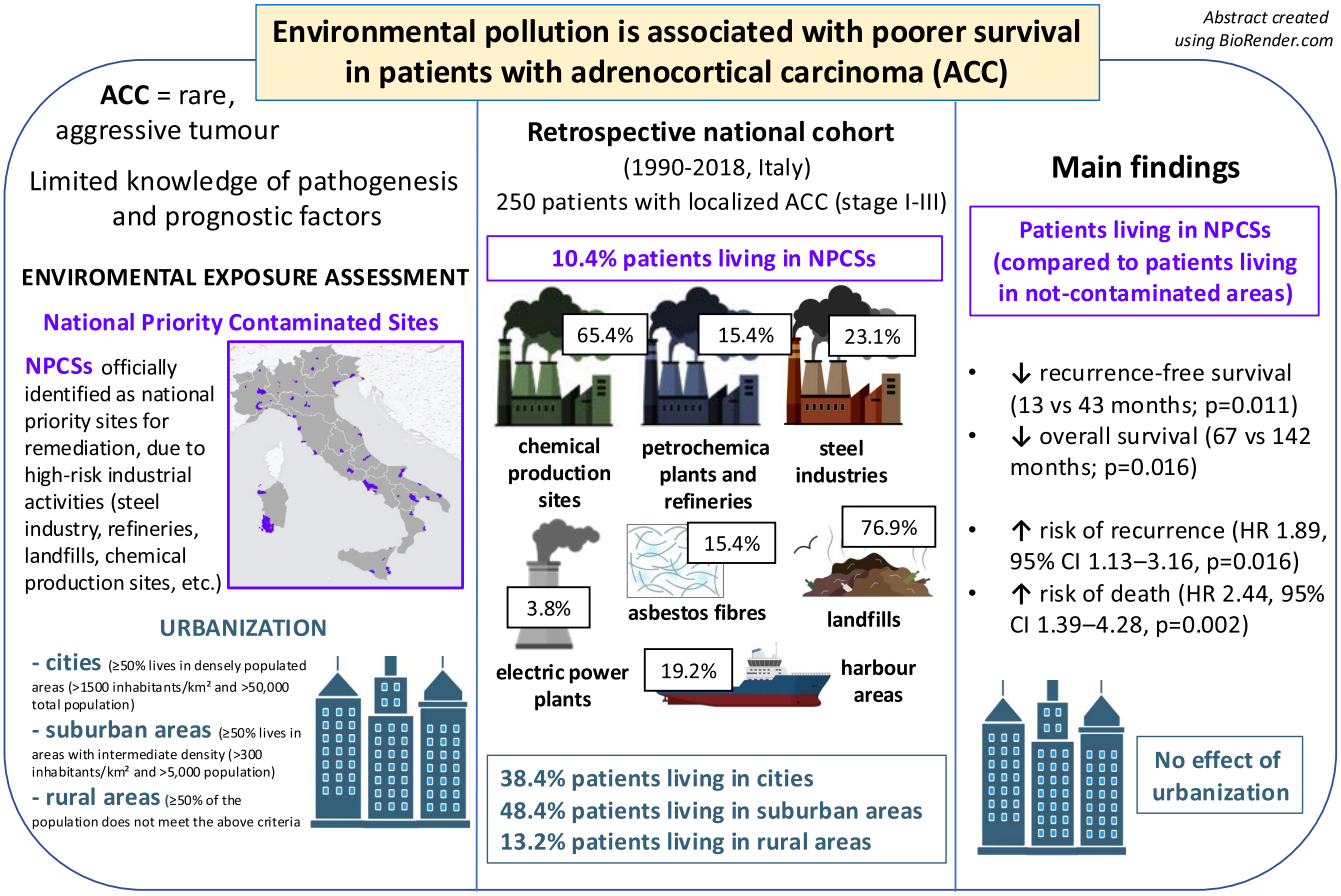
environmental exposures may contribute to the disease behaviour, highlighting a new direction for integrated epidemiological and biological research.

Keywords pollution, survival, outcome, progression, adrenal, cancer

Significance

The contribution of environmental pollution exposure to the clinical behaviour of adrenocortical carcinoma (ACC) remains poorly understood. In this nationwide multicentre cohort study, we found that residence in officially designated environmentally contaminated areas was independently associated with shorter recurrence-free and overall survival in patients with localized ACC, whereas no association was observed with the level of urbanization. These findings provide the first clinical evidence linking environmental contamination with prognosis in adult patients with ACC. Although the observational design of our study does not allow causal inference, our results support the need to consider environmental contamination as a possible prognostic factor and fuel future studies integrating environmental exposure assessment with genomic profiling to better understand ACC behaviour.

Graphical abstract



Introduction

Adrenocortical carcinoma (ACC) is a rare endocrine tumour of the adrenal cortex characterized by a remarkable pathological variability and heterogeneous prognosis,[1] with an estimated annual incidence of 0.7 to 2 cases per million individuals.[2-5] Due to the rarity of ACC, knowledge of its pathogenetic mechanisms and natural course of the disease remains limited.

ACC can occur in hereditary disorders such as Li-Fraumeni, Beckwith-Wiedemann, multiple endocrine neoplasia type 1 (MEN1), and Lynch syndromes. However, most cases of ACC are sporadic.[6,7] In the last decade, studies on apparently sporadic ACC have reported alterations in genes mainly involved in cell determination, proliferation and migration (*ZNRF3* and *CTNNB1*), cell cycle regulation (*TP53*, *CDKN2a* and *RB1*), chromatin remodelling (*MEN1*) and maintenance of chromosome length (*TERT* and *TERF2*).[7-10]

Interestingly, one of these studies showed that a subset of ACCs displays mutational patterns that partially overlap with those typically found in cancers linked to environmental

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carcinogens, including melanoma and lung cancer. Although no specific environmentally driven pathway has been identified in ACC, these findings suggest that environmental exposures might contribute to ACC development, potentially in combination with genetic susceptibility.[10]

The hypothesis of a gene–environment interaction in the pathogenesis of ACC is supported by epidemiological data from southern Brazil, where a high incidence of paediatric ACC has been associated with the widespread *TP53 R337H* germline mutation. In this setting, Costa et al. observed that the carriers of this mutation residing in industrialized areas had a significantly higher risk of developing ACC compared to those living in agricultural regions. Their findings suggested that environmental exposure may modulate disease penetrance in genetically predisposed individuals.[11]

Research on the impact of pollution on cancer is increasing. There is accumulating evidence that environmental pollutants, including industrial chemicals, pesticides, and airborne toxins, are major contributors to carcinogenesis in various tumour types.[12,13] Exposure to air pollutants has also been linked to an increased risk of lung cancer,[14,15] while endocrine-disrupting chemicals (EDCs), such as bisphenol A and phthalates, have been associated with hormone-dependent cancers, including breast and prostate cancer.[16] Recently, less intuitive and straightforward associations have been demonstrated, such as the effect of air pollution on survival in patients with colorectal cancer.[17]

The relationship between environmental pollution and ACC in adult patients, however, has been largely unexplored. We therefore evaluated the clinical characteristics and survival outcomes of a national cohort of adult patients with ACC, stratified according to environmental exposure based on their area of residence.

Patients and methods

Patients

This was a retrospective analysis based on a multicentre cohort of patients in Italy with histologically confirmed ACC, whose baseline characteristics and clinical management were reported in a recent publication.[18] The cohort included patients diagnosed between January 1990 and June 2018, and followed at 12 tertiary referral centres across Italy.

For the present study, a subset of patients was selected from this cohort, based on predefined inclusion and exclusion criteria aimed at ensuring data completeness for survival and environmental analyses.

The following inclusion criteria were applied: age ≥18 years at the time of ACC diagnosis; residence in Italy at the time of diagnosis; histological confirmation of ACC; availability of complete data for the following variables: (1) age at diagnosis; (2) mode of tumour detection (incidentaloma vs symptomatic); (3) hormone secretory profile; (4) ENSAT tumour stage; and (5) Ki67 proliferation index (only for patients with ENSAT stage I-III).

The following exclusion criteria were applied: age <18 years at diagnosis (to prevent the confounding effect of hereditary predisposition, which is more frequent in paediatric ACC); residence outside Italy at diagnosis; missing data on any of the variables listed above.

The following data were collected: sex; age at diagnosis; date of diagnosis; municipality of residence at diagnosis (used for classification of environmental exposure); mode of tumour detection (serendipitous discovery vs symptomatic presentation due to mass effect, hormone excess or constitutional symptoms); hormone secretory profile [non-secreting; cortisol ± other hormones; other secretion, referring to tumours producing hormones other than cortisol (eg, androgens, oestrogens, or mineralocorticoids)]; tumour size; ENSAT stage; pathological features, including resection status (R0, R1, RX, R2), Weiss score, and Ki67 index; adjuvant mitotane therapy; and data on recurrence and death.

Information on residence at diagnosis was collected for all patients. Data on changes of residence within the previous 5 years were recorded when available, although not systematically verifiable due to the retrospective design.

The S-GRAS score was calculated according to the original definition[19] which integrates tumour stage, Ki67 index, resection status, age, and symptoms at presentation.

For descriptive purposes, patients were categorized as low-risk (S-GRAS <4) or high-risk (S-GRAS ≥4).

Information on additional primary malignancies was also collected.

Recurrence was defined as the first radiologically confirmed appearance of a new lesion at contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) after primary tumour resection. Surveillance protocols varied slightly between centres, with imaging intervals during follow-up ranging from 3 to 6 months.

The study was approved by the local ethics committee (*Comitato Etico Interaziendale A.O.U. San Luigi Gonzaga di Orbassano—AA.SS.LL. TO3, TO4, TO5*; approval number: 8701, dated June 19, 2020) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained as appropriate. Patient information was pseudonymized, and measures were implemented to prevent duplicate entries for individuals followed at multiple centres. The database was locked for analysis on August 31, 2023.

Exposure to environmental pollutants

To evaluate the potential impact of environmental contamination, patients were stratified according to two distinct types of exposure based on their municipality of residence at the time of ACC diagnosis: (i) residence in National Priority Contaminated Sites (NPCSs) vs non-contaminated sites, and (ii) level of urbanization. These two variables were analysed separately to prevent collinearity.

The NPCSs are areas identified by the Italian Ministry of Environment as national priority sites for environmental remediation, based on the extent of contamination, health risk, and the complexity of clean-up interventions.[20] These sites, which are found all over Italy (Figure 1), have been contaminated due to the presence of high-risk industrial activities, including petrochemical plants, refineries, steel industries, chemical production sites, electric power plants, harbour areas, mines, quarries, asbestos extraction or processing sites, landfills, and incinerators.[21] Given the heterogeneity of these

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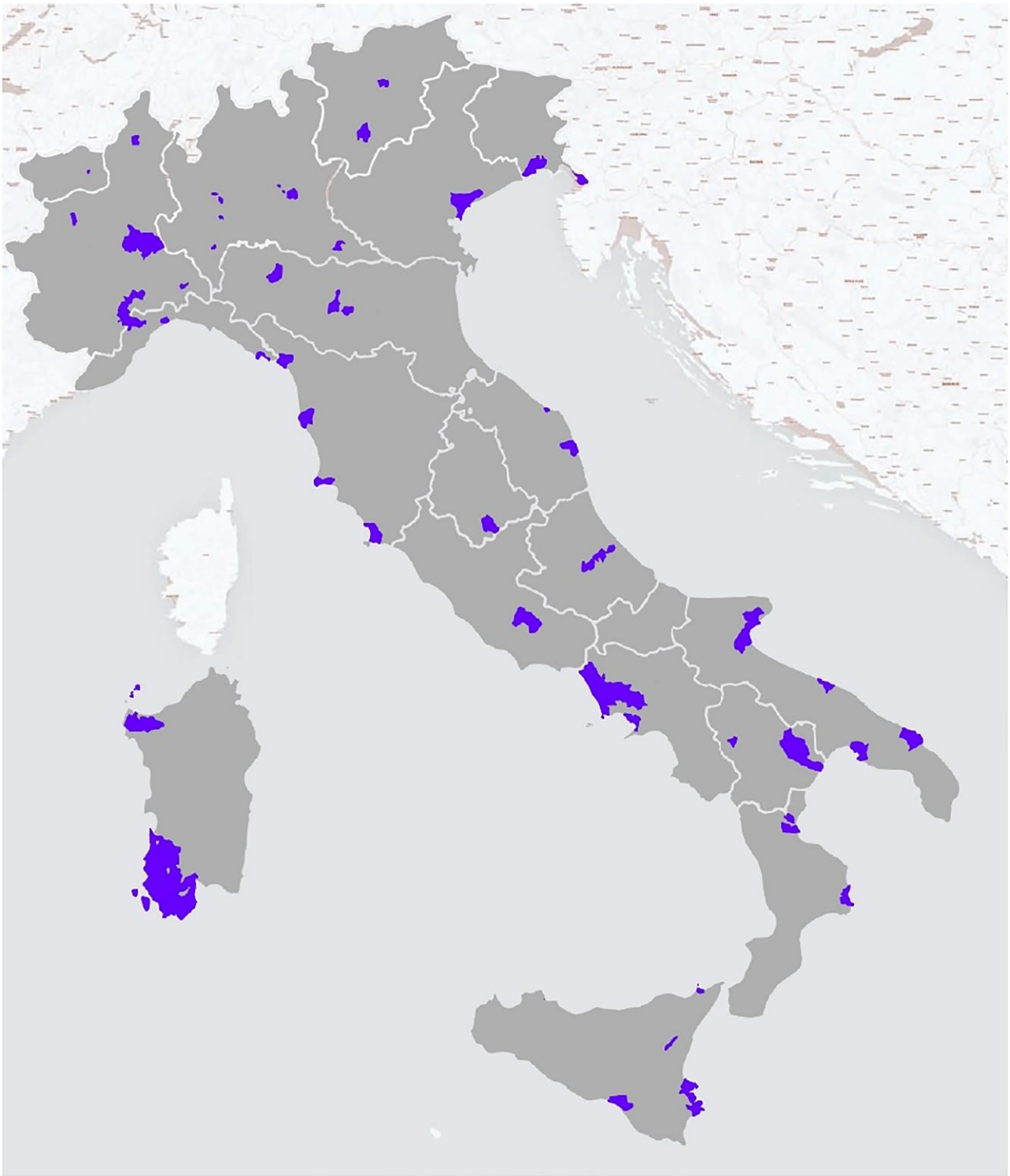

Figure 1 Map of Italy showing the national priority contaminated sites (NPCSs). *Figure adapted from the Fifth SENTIERI Report.*

sources, this classification does not allow attribution to a single type of pollutant or exposure pathway, but rather reflects complex environmental contamination. Exposure was defined at the municipality level based on official national classifications,[21] and all residents within municipalities included in NPCSs were considered exposed, without further spatial refinement.

The level of urbanization was used as an indirect indicator of exposure to outdoor air pollutants and was therefore considered a contextual proxy, although it does not capture individual-level exposure or specific pollutant concentrations. Municipalities were classified into three categories (cities, towns/suburbs, and rural areas) according to the criteria defined by Eurostat

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and EU Regulation 2017/2391.[22] This categorization is based on both population density and total population size: "cities" are defined as municipalities where ≥50% of the population lives in densely-populated areas (>1500 inhabitants/km^2 and >50 000 total population); "towns and suburbs", where ≥50% of the population lives in areas with intermediate density (>300 inhabitants/km^2 and >5000 population); and "rural areas", where ≥50% of the population does not meet the above criteria.

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as medians and interquartile ranges (IQRs). Differences between groups were tested using the χ^2 test for categorical variables, and the Mann–Whitney U test for continuous variables.

Survival outcomes were analysed using the Kaplan–Meier method with 95% confidence intervals (CIs). Recurrence-free survival (RFS) was defined as the time from diagnosis to the first radiological evidence of recurrence. Overall survival (OS) was defined as the time from diagnosis to death from any cause. In patients with localized disease, the date of surgery was considered as the date of diagnosis. Patients without recurrence or death were censored at the last available follow-up. To mitigate immortal time bias, a 3-month landmark approach was applied to survival analyses.

Multivariable Cox proportional hazards regression models were used to identify prognostic factors. In order to prevent mutual confounding of variables concerning exposure to pollutants, two separate primary multivariable analyses were performed: one including residence in NPCSs, and the other including the level of urbanization. All models were adjusted for: age, tumour stage, mode of detection (incidentaloma vs symptomatic), cortisol secretion, resection status, and Ki67 index.

Because mode of tumour detection may act either as a confounder related to healthcare access, sensitivity analyses were performed by repeating the multivariable models after excluding this variable.

In addition to the primary multivariable models, a more parsimonious Cox proportional hazards model was constructed as a sensitivity analysis. In this model, residence in NPCSs (or level of urbanization) was evaluated together with the S-GRAS score, which integrates tumour stage, Ki67 index, resection status, age, and symptoms at presentation, thus reducing the number of covariates while preserving prognostic information. Finally, exploratory stratified analyses were conducted within low-risk (S-GRAS <4) and high-risk (S-GRAS ≥4) subgroups to assess whether the association between residence in NPCSs and survival outcomes differed according to baseline prognostic risk.

To assess the robustness of the findings to centre-level heterogeneity and to changes in ACC management over the 1990-2018 study period, we performed a series of pre-specified sensitivity analyses on the primary Cox model. Centre effects were addressed in three complementary ways: (1) stratification by centre, allowing a separate baseline hazard for each centre while sharing covariate effects, (2) a shared frailty Cox model with a gamma-distributed centre random effect, and (3) a mixed-effects Cox model with a Gaussian random intercept on centre, providing a complementary parameterization of unobserved between-centre heterogeneity on the log-hazard scale. Calendar time was modelled both as a continuous variable (year of diagnosis) and, in a parallel specification, as a categorical variable. Joint specifications combining each centre adjustment (stratification, gamma frailty, or Gaussian random intercept) with calendar-period adjustment were also fitted to address both sources of variability simultaneously. The proportional hazards assumption was verified under each specification by inspection of scaled Schoenfeld residuals. All analyses were performed in R (version 4.5.0) using the survival and coxme packages. A *P*-value <.05 was considered as statistically significant.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

General characteristics of the study population

The study population included 336 adult patients with apparently sporadic ACC (Figure 2). Of these, 250 patients had localized disease (stage I-III) and 86 had metastatic disease (stage IV).

The general characteristics of the study population are reported in Table 1.

Given the substantial prognostic differences between these two groups, all analyses were conducted separately for localized and advanced ACC. However, due to the limited number of patients in the metastatic group, when the environmental subgroups were considered (eg, only 5 patients residing in NPCSs and 12 in rural areas), detailed stratified analyses were reported only for patients with localized disease (stage I-III).

A comparison between included and excluded patients with localized disease by centre and calendar period is provided in Table S1.

Recurrence status was available for 237/250 patients with localized disease, and among these, recurrence occurred in 143/237 (60.3%).

For RFS analyses, patients with missing information on the date of recurrence ($n = 8$) were excluded. The 5-year RFS was 42.7% (95% CI 36.6%-49.8%), and the median RFS was 33 months (95% CI 25-60).

In the same cohort, death occurred in 40.4% of patients, and in nine cases (3.6%) due to causes other than tumour progression. Complete information on vital status and date of death was available for all patients. The 5-year OS was 67.4% (95% CI 61.4%-74.0%) and the median OS was 134 months (95% CI 101-177). The median follow-up estimated by the reverse Kaplan–Meier method was 98 months (95% CI 83-104).

Stratification according to residence in NPCSs

The cohort of cases with localized disease (stage I-III) included 26 (10.4%) patients residing in areas defined as NPCSs and 224 (89.6%) in non-contaminated areas.

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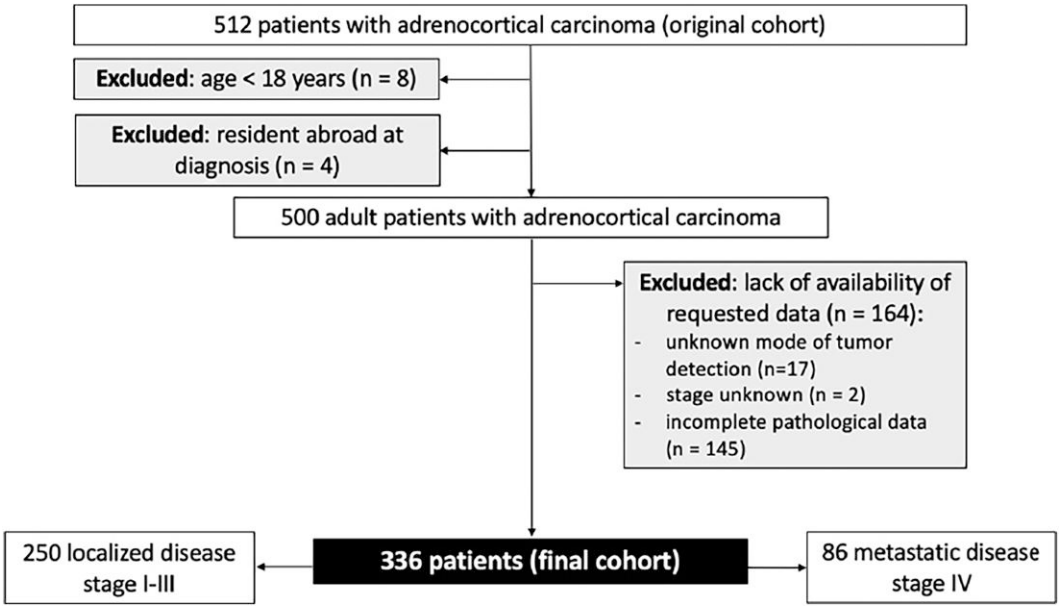

Figure 2 Participants in the study.

According to the fifth SENTIERI report,[21] patients residing in NPCSs were found to be exposed to different sources of environmental pollution, including landfills (76.9%), chemical production sites (65.4%), steel industries (23.1%), petrochemical plants and refineries (15.4%), asbestos fibres (15.4%), harbour areas (19.2%), and electric power plants (3.8%) (Figure 3). The geographical distribution of patients and the corresponding environmental source categories in their areas of residence are shown in Figure S1.

In patients living in NPCSs, ACC more frequently presented with symptomatic disease (22/26, 84.6%) compared with patients from non-contaminated areas (121/224, 54.0%), whereas incidental presentation was less frequent (4/26, 15.4% vs 103/224, 46.0%; $P = .006$). However, the two groups had similar characteristics in terms of sex distribution, age, ENSAT tumour stage, secretion pattern, resection status, Ki67% values, and use of adjuvant mitotane treatment (Table 2).

The median RFS was significantly shorter in patients living in NPCSs than in those from non-contaminated sites (13 months, 95% CI 9-31 vs 43 months, 95% CI 28-83, $P = .011$) (Figure 4A). At 5 years, the RFS rate was lower in patients residing in NPCSs compared to those in non-contaminated sites (24%, 95% CI 11.9%-48.2% vs 45%, 95% CI 38.5%-52.7%, log-rank test P-value = .009).

The median OS was significantly shorter in patients living in NPCSs than in those living in non-contaminated sites (67 months, 95% CI 36–not reached vs 142 months, 95% CI 127-177, $P = .016$) (Figure 4B). At 5 years, the estimated survival rate was lower in patients residing in NPCSs compared to those in non-contaminated sites (59.1%, 95% CI 42.5%-82.3% vs 68.4%, 95% CI 62.0%-75.4%, log-rank test P-value = .02).

Among patients residing in NPCSs, 3/26 (11.5%) had a history of a previous malignancy at the time of ACC diagnosis, whereas no new primary tumours were recorded during follow-up. In patients from non-contaminated areas, 13/224 (5.8%) had a previous malignancy at diagnosis and 15/224 (6.7%) developed a new primary tumour during follow-up (Table S2).

Stratification according to residence in areas with different levels of urbanization

The cohort of patients with localized disease (stage I-III) included 96 patients (38.4%) living in cities, 121 (48.4%) in towns and suburban areas, and 33 (13.2%) in rural areas. The three groups showed no significant differences in terms of sex, age at diagnosis, and the other major prognostic factors. Conversely, a different hormone secretion pattern was observed, with a lower frequency of cortisol-secreting tumours and a higher prevalence of other types of secretion, above all androgens, in rural areas (Table 3).

The median RFS was 27 months (95% CI 19-102) in cities, 33 months (95% CI 21-108) in suburban areas, and 71 months (95% CI 30–not reached) in rural areas. The Kaplan–Meier curves showed no statistically significant differences among the groups (log-rank test, $P = .685$). At 5 years, the RFS rate was 41.7% (95% CI 32.2%-54.0%) in cities, 41.1% (95% CI 32.7%-51.7%) in suburban areas, and 51.0% (95% CI 35.9%-72.3%) in rural areas (Figure 5A).

The median OS was 127 months (95% CI 67–not reached) in cities, 163 months (95% CI 127–not reached) in suburban areas, and 142 months (95% CI 50–not reached) in rural areas. No statistically significant differences were observed among the groups (log-rank test, $P = .556$). At 5 years, the estimated OS rate was 65.5% (95% CI 55.8%-76.8%) in cities, 70.0% (95% CI 61.7%-79.5%) in suburban areas, and 63.8% (95% CI 48.8%-83.5%) in rural areas (Figure 5B).

Prognostic models

To investigate prognostic factors in localized ACC, two separate multivariable Cox regression analyses were performed for both RFS and OS. One model included residence in NPCSs among the covariates, while the other model included the level of urbanization, ie, whether the patient resided in a city, suburban, or rural area.

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Table 1 General characteristics of study population.

Characteristics	Entire cohort N = 336	Localized disease N = 250	Metastatic disease N = 86
Sex, *N* (%)			
Valid N	*336*	*250*	*86*
Male	134 (39.9%)	102 (40.8%)	32 (37.2%)
Female	202 (60.1%)	148 (59.2%)	54 (62.8%)
Age, year			
Valid N	*336*	*250*	*86*
Median (IQR)	49 (38-59)	50.0 (39-59)	45.5 (38-59)
Incidentaloma, *N* (%)			
Valid N	*336*	*250*	*86*
Yes	126 (37.5%)	107 (42.8%)	19 (22.1%)
No	210 (62.5%)	143 (57.2%)	67 (77.9%)
Tumour size, cm			
Valid N	*336*	*250*	*86*
Median (IQR)	10 (7-14)	9.8 (6.6-13)	12 (10-17)
Hormone secretion, N (%)			
Valid N	*336*	*250*	*86*
Non–secreting	158 (47.0%)	130 (52.0%)	28 (32.6%)
Cortisol ± other hormones	142 (42.3%)	97 (38.8%)	45 (52.3%)
Other secretion[a]	36 (10.7%)	23 (9.2%)	13 (15.1%)
Tumour stage, *N* (%)			
Valid N	*336*	*250*	*86*
Stage I–II	194 (57.7%)	194 (77.6%)	—
Stage III	56 (16.7%)	56 (22.4%)	—
Stage IV	86 (25.6%)	—	86 (100%)
Weiss score			
Valid N	*277*	*250*	*27*
Median (IQR)	6 (5-7)	6 (5-7)	6 (5-7)
Ki67, (%)			
Valid N	*279*	*250*	*29*
Median (IQR)	18 (7-30)	15 (6-29)	32 (15-40)
Resection status, *N* (%)			
Valid N	*329*	*243*	
R0	183 (55.6%)	174 (71.6%)	—
R1	20 (6.1%)	16 (6.6%)	—
R2	37 (11.2%)	5 (2.1%)	—
Rx	89 (27.1%)	48 (19.7%)	—
Adjuvant therapy, *N* (%)			
Valid N	*270*	*244*	*26*
None	93 (34.5%)	86 (35.2%)	7 (26.9%)
Mitotane	162 (60.0%)	157 (64.4%)	5 (19.2%)
Chemotherapy	13 (4.8%)	0 (0.0%)	13 (50.0%)
Radiotherapy	2 (0.7%)	1 (0.4%)	1 (3.9%)

Abbreviation: IQR, interquartile range: *N*, number of patients. Values in italics indicate the number of cases with available data.
[a]Other secretion: androgens, oestrogens, mineralocorticoids.

This approach was used to prevent collinearity or confounding effects between two variables concerning exposure to pollutants.

Regarding RFS, in the first model, high Ki67 index (HR 1.03 per unit increase, 95% CI 1.02-1.04, $P < .001$), cortisol secretion (HR 1.47, 95% CI 1.02-2.10, $P = .038$), and microscopic residual disease (R1 vs R0: HR 1.96, 95% CI 1.01-3.82, $P = .047$), as well as residence in NPCSs (HR 1.89, 95% CI 1.13-3.16, $P = .016$) were independently associated with a shorter RFS (Table 4).

In the model including urbanization, a higher Ki67 (HR 1.03 per unit increase, 95% CI, 1.02-1.04, $P < .001$) and microscopic residual disease (R1 vs R0: HR 1.96, 95% CI 1.01-3.83, $P = .048$) were independently associated with an increased recurrence risk. On the other hand, incidentaloma presentation (HR 0.63, 95% CI 0.42–0.92, $P = .018$) was associated with a lower risk, while no statistically significant association was found between urbanization and RFS (Table 5).

Regarding OS, in the first model a higher Ki67 index (HR 1.03, 95% CI 1.02-1.04, $P < .004$), older age at diagnosis (HR 1.03 per year, 95% CI 1.01-1.04, $P = .004$), stage III disease (HR 1.69, 95% CI 1.08-2.65, $P = .021$), residual disease after surgery (R1 vs R0: HR 2.49, 95% CI 1.22-5.11, $P = .012$; R2 vs R0: HR 4.74, 95% CI 1.66-13.54, $P = .004$) and cortisol secretion (HR 1.69, 95% CI 1.11-2.58, $P = .015$) were independently associated with increased mortality. In addition, residence in NPCSs was significantly associated with worse OS (HR 2.44, 95% CI 1.39-4.28, $P = .002$) (Table 6).

In the model including urbanization, there were similar associations for Ki67 (HR 1.03 per unit increase, 95% CI 1.02-1.04, $P < .001$), age at diagnosis (HR 1.02 per year, 95% CI 1.01-1.04, $P = .006$), stage III (HR 1.69, 95% CI 1.08-2.66, $P = .022$, residual disease after surgery (R1 vs R0: HR 2.74, 95% CI 1.33-5.64, $P = .006$; R2 vs R0: HR 5.08, 95% CI 1.74-14.84, $P = .003$), and cortisol secretion (HR 1.59, 95% CI 1.04-2.42, $P = .033$). The level of urbanization was not significantly associated with OS (Table 7).

In sensitivity analyses excluding mode of detection, the association between residence in NPCSs and both RFS and overall survival remained consistent (Table S3 and S4), while no association was observed for level of urbanization, confirming the primary findings (Table S5 and S6).

Finally, more parsimonious multivariable Cox models were constructed combining the exposure variable (residence in NPCSs or urbanization levels) with the S-GRAS score.

In this model (Table S7), residence in NPCSs remained independently associated with shorter RFS (HR 1.89, 95% CI 1.16-3.08, $P = .011$) and overall survival (HR 1.83, 95% CI 1.07-3.14, $P = .027$). In exploratory stratified analyses, the association between residence in NPCSs and recurrence was particularly evident among high-risk patients (S-GRAS ≥4) (log-rank $P = .037$) (Figure S2), whereas no significant difference was observed among low-risk patients (S-GRAS <4) (log-rank $P = .098$) (Figure S3). A similar pattern was observed for overall survival, with a significant separation of curves among high-risk patients (log-rank $P = .025$) (Figure S4), but not among low-risk patients (log-rank $P = .5$) (Figure S5).

In contrast, when the same parsimonious multivariable model was applied to urbanization levels, no independent association with either recurrence-free or overall survival was observed (Table S8).

The association between NPCS and OS/RFS was robust to all sensitivity specifications addressing centre-level heterogeneity and calendar-time effects. For RFS, the adjusted hazard ratio for NPCS remained statistically significant in the Cox model stratified by centre with calendar-period adjustment (HR = 1.83, 95% CI 1.07-3.11), in the shared gamma-frailty model

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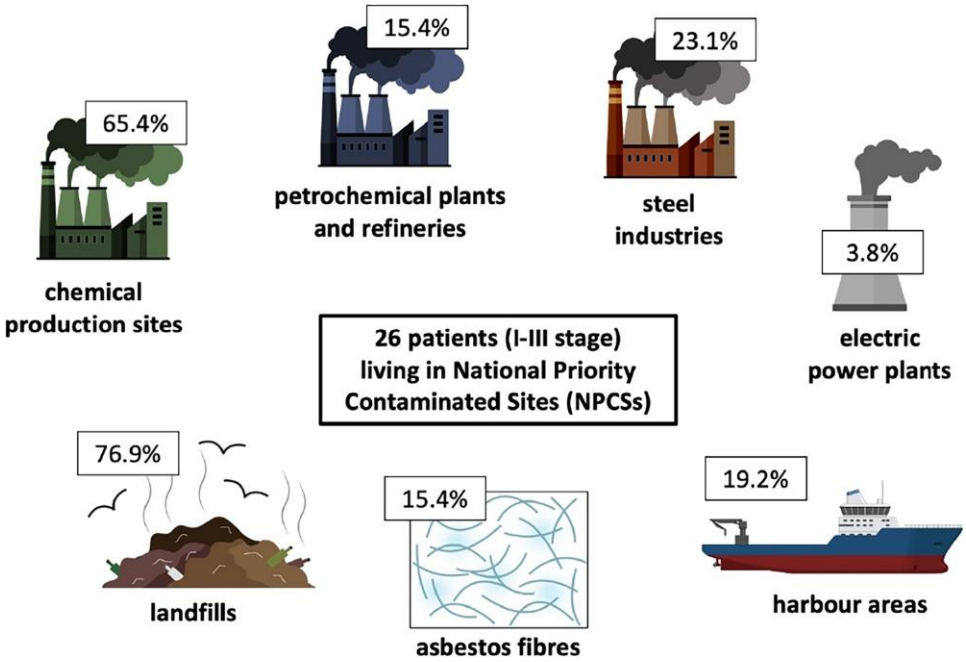

Figure 3 Sources of environmental pollution for the 26 patients with localized ACC living in national priority contaminated sites (NPCSs). Categories are not mutually exclusive, as several contamination sources may coexist within the same area. *Figure created using BioRender.com.*

(HR = 1.84, 95% CI 1.08-3.12), and in the mixed-effects Cox model with a Gaussian centre random intercept (HR = 1.84, 95% CI 1.08-3.12). The estimated between-centre frailty variance was non-negligible (gamma frailty $\theta = 0.279$, $P < .001$; Gaussian random-intercept variance = 0.335 (SD = 0.579)). Crucially, the NPCS effect maintained comparable magnitude. Modelling calendar time as a continuous year of diagnosis rather than as a categorical period yielded consistent estimates. Full results of the sensitivity analyses are reported in Table S9 and S10.

Discussion

In this nationwide cohort of adult patients with ACC, we investigated the impact of environmental pollution on disease presentation and outcome. Our analysis revealed that residence in areas, defined in Italy as NPCSs was associated with both a higher recurrence rate and reduced overall survival in patients with localized ACC. This association remained significant after adjustment for age, tumour stage, resection status, Ki67 index, hormone secretion, and mode of presentation. Importantly, this association persisted in more parsimonious models incorporating the S-GRAS score as a composite prognostic variable. Furthermore, stratified analyses suggested that the association between residence in NPCSs and recurrence and mortality was particularly evident among high-risk patients, whereas no statistically significant difference was observed among low-risk patients. Although these subgroup findings should be interpreted cautiously, they may suggest that environmental exposure could exacerbate tumour aggressiveness in biologically unfavourable disease. In addition, tumours in the NPCS group were more frequently symptomatic at diagnosis, which suggests a more aggressive clinical behaviour.

Although causality cannot be inferred from our observational data, several experimental findings provide a biological framework that may help in explaining the association observed in our cohort. It is well-known that the adrenal cortex is a susceptible target for EDCs, due to its lipophilic nature and its high expression of steroidogenic cytochrome P450 enzymes involved in both steroid biosynthesis and xenobiotic metabolism.[23] Accordingly, studies using the H295R human adrenocortical cell line have demonstrated that several environmental contaminants, including persistent organic pollutants such as polychlorinated biphenyls (PCBs), can alter steroidogenesis and protein expression through activation of aryl hydrocarbon receptor-related pathways, as well as other pathways involved in cellular stress responses, apoptosis and metabolic regulation.[24,25] In addition, recent genomic studies have considerably expanded our understanding of ACC biology, demonstrating that aggressive tumours are characterized by recurrent alterations involving TP53, cell-cycle regulation, DNA repair pathways, and genomic instability, all of which have been implicated in tumour progression and clinical heterogeneity.[26,27] Although the impact of environmental exposure on these molecular pathways or mutational signatures in ACC remains unknown, a proof of principle for a gene–environment interaction comes from paediatric ACC. In southern Brazil, Costa et al.[11] demonstrated that environmental exposure may modulate the penetrance of the *TP53 R337H* germline pathogenic variant.

In contrast, studies addressing environmental factors in adult sporadic ACC are extremely limited. To the best of our knowledge, this is the first clinical study in adult ACC patients to report an association between pollutant exposure and survival. To date, only two studies have explored the potential relationship between geographic or environmental factors and ACC, and both focused on incidence patterns rather than clinical outcomes.[28,29] A registry-based study analysed the ACC incidence across

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Table 2 Characteristics of patients with localized disease, broken down by residence in national priority contaminated sites (NPCSs) and non–contaminated areas.

Characteristics	NPCSs *N* = 26	Non-contaminated areas *N* = 224	*P* value
Age, year			
Valid N	*26*	*224*	.115
Median (IQR)	44.5 (26.2-58)	50.0 (39.8-59)	
Sex, *N* (%)			
Valid N	*26*	*224*	.190
Male	7 (26.9%)	95 (42.4%)	
Female	19 (73.1%)	129 (57.6%)	
Tumour stage, *N* (%)			
Valid N	*26*	*224*	1.000
Stage I–II	20 (76.9%)	174 (77.7%)	
Stage III	6 (23.1%)	50 (22.3%)	
Tumour size, cm			
Valid N	*26*	*224*	.526
Median (IQR)	8 (7-11.2)	10 (6.5-13.2)	
Hormone secretion, *N* (%)			
Valid N	*26*	*224*	.117
Non–secreting	10 (38.5%)	120 (53.6%)	
Cortisol ± other hormones	11 (42.3%)	86 (38.4%)	
Other secretion[a]	5 (19.2%)	18 (8.0%)	
Incidentalomas, *N* (%)			
Valid N	*26*	*224*	.006
Yes	4 (15.4%)	103 (46.0%)	
No	22 (84.6%)	121 (54.0%)	
Weiss score			
Valid N	*26*	*224*	.335
Median (IQR)	6 (5-7)	6 (5-8)	
Ki67, (%)			
Valid N	*26*	*224*	.377
Median (IQR)	16.5 (8.5-33.8)	15 (6-26)	
Resection status, *N* (%)			
Valid N	*26*	*217*	.667
R0	17 (65.4%)	157 (72.3%)	
R1	2 (7.7%)	14 (6.5%)	
R2	0 (.0%)	5 (2.3%)	
RX	7 (26.9%)	41 (18.9%)	
S-GRAS category, *N* (%)			
Valid N	*26*	*224*	.37
Low-risk patients	12 (46.2%)	124 (55.4%)	
High-risk patients	14 (53.8%)	100 (44.6%)	
Adjuvant therapy, N (%)			
Valid N	*26*	*218*	.449
None	12 (46.2%)	74 (33.9%)	
Mitotane	14 (53.8%)	143 (65.6%)	
Radiotherapy	0 (0.0%)	1 (0.5%)	
Recurrences, N (%)	20 (76.9%)	123 (58.3%)	
Valid N	*26*	211	
Deaths, *N* (%)	16 (61.5%)	85 (37.9%)	
Valid N	*26*	*224*	

Abbreviation: IQR, interquartile range. N, number of patients. Values in italics indicate the number of cases with available data.
[a]Other secretion: androgens, oestrogens, mineralocorticoids.

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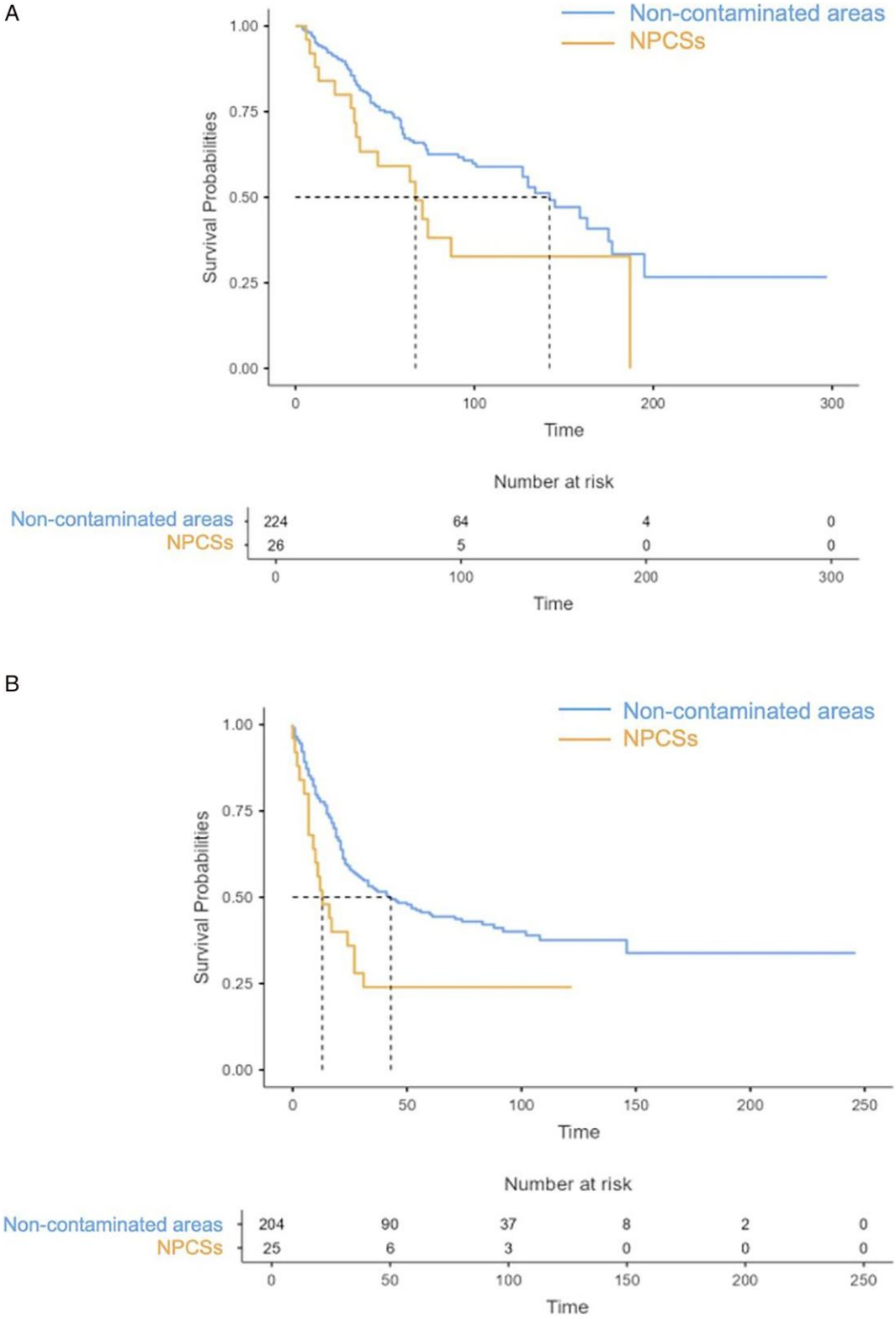

Figure 4 The Kaplan–Meier curves for recurrence free survival (A) and overall survival (B) in patients with localized disease according to residence in national priority contaminated sites (NPCSs) and non–contaminated areas. To mitigate immortal time bias, a 3–month landmark approach was applied to survival analyses.

counties in Texas over a 19 year period and failed to identify any geographic clustering of the 448 ACC cases reported[28] . Although environmental factors such as proximity to power plants were explored, no direct exposure assessment or outcome analysis was performed. More recently, Holmstoen et al. analysed ACC cases from both a tertiary referral centre and the Colorado Central Cancer Registry and found a twofold higher incidence of ACC in western vs eastern Colorado.[29] The authors hypothesized that

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Table 3 Characteristics of patients with localized disease, broken down by residence in areas with different levels of urbanization.

Characteristics	Cities *N* = 96	Suburban areas *N* = 121	Rural areas *N* = 33	*P* value
Age, year				
Valid N	*96*	*121*	*33*	.490
Median (IQR)	49.5 (36.8-58.0)	49.0 (39-58)	54 (43-60)	
Sex, N (%)				
Valid N	*96*	*121*	*33*	.516
Male	43 (44.8%)	45 (37.2%)	14 (42.4%)	
Female	53 (55.2%)	76 (62.8%)	19 (57.6%)	
Tumour stage, *N* (%)				
Valid N	*96*	*121*	*33*	.815
Stage I-II	73 (76%)	96 (79.3%)	25 (75.8%)	
Stage III	23 (24%)	25 (20.7%)	8 (24.2%)	
Tumour size, cm				
Valid N	*96*	*121*	*33*	.310
Median (IQR)	9 (6.9-12)	10 (6.5-13)	10 (7.8-15)	
Hormone secretion, *N* (%)				
Valid N	*96*	*121*	*33*	.024
Non–secreting	49 (51.1%)	65 (53.7%)	16 (48.5%)	
Cortisol ± other hormones	39 (40.6%)	49 (40.5%)	9 (27.3%)	
Other secretion[a]	8 (8.3%)	7 (5.8%)	8 (24.2%)	
Incidentalomas, *N* (%)				.377
Valid N	*96*	*121*	*33*	
Yes	43 (44.8%)	47 (38.8%)	17 (51.5%)	
No	53 (55.2%)	74 (61.2%)	16 (48.5%)	
Weiss score				
Valid N	*96*	*121*	*33*	.572
Median (IQR)	6 (5-7)	6 (5-8)	6 (5-7.8)	
Ki67, (%)				
Valid N	*96*	*121*	*33*	.908
Median (IQR)	15.0 (6-30)	17 (6-25)	18 (10-30)	
Resection status, *N* (%)				
Valid N	*92*	*118*	*33*	.088
R0	72 (78.3%)	76 (64.4%)	26 (78.8%)	
R1	5 (5.4%)	9 (7.6%)	2 (6.1%)	
R2	0 (0%)	3 (2.5%)	2 (6.1%)	
RX	15 (16.3%)	30 (25.4%)	3 (9.1%)	
S-GRAS category, *N* (%)				
Valid N	*96*	*121*	*33*	
Low-risk patients	56 (58.3%)	62 (51.2%)	18 (54.5%)	
High-risk patients	40 (41.7%)	59 (48.8%)	15 (45.5%)	
Adjuvant therapy, *N* (%)				
Valid N	*93*	*118*	*244*	.698
None	32 (34.4%)	44 (37.3%)	10 (30.3%)	
Mitotane	60 (64.5%)	74 (62.7%)	23 (69.7%)	
Radiotherapy	1 (1.1%)	0 (0%)	0 (0%)	
Recurrences, *N* (%)	55 (61.1%)	69 (60.5%)	19 (57.6%)	
Valid N	*90*	*114*	*33*	
Deaths, *N* (%)	42 (43.8%)	45 (37.2%)	14 (42.4%)	
Valid N	*96*	*121*	*33*	

Abbreviation: IQR, interquartile range. *N*, number of patients. Values in italics indicate the number of cases with available data.
[a]Other secretion: androgens, oestrogens, mineralocorticoids.

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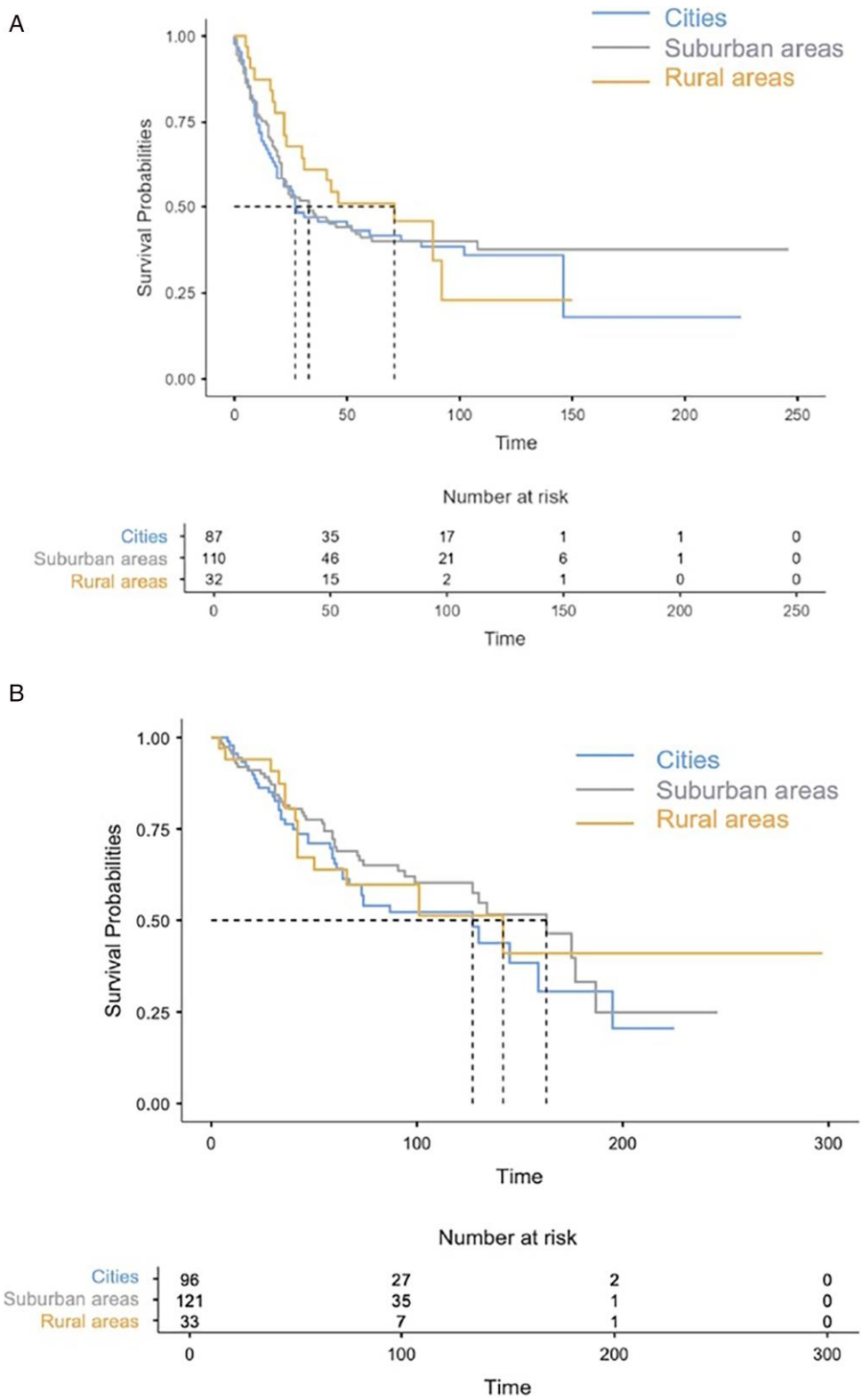

Figure 5 Kaplan–Meier curves for recurrence free survival (A) and overall survival (B) in patients with localized disease according to residence in areas with different levels of urbanization. To mitigate immortal time bias, a 3–month landmark approach was applied to survival analyses.

regional environmental or occupational exposures (such as those related to mining or agriculture) may have contributed to this difference, although no specific contaminant was identified. Unlike these studies that focus on tumour incidence, to the best of our knowledge our analysis is the first to integrate individual-level clinical outcome data with geographically defined environmental exposure categories in adult patients with ACC, and to show that residence in contaminated sites is associated with higher

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Table 4 Multivariable analysis of prognostic factors for recurrence-free survival in patients with localized disease, including residence in national priority contaminated sites (NPCSs).

	Recurrence-free survival		
Factor	HR	95% CI	*P* value
Age at diagnosis	1.01[a]	1.00-1.02	.215
ENSAT tumour stage[b]	1.33	0.87-2.04	.193
Cortisol secretion[c]	1.47	1.02-2.10	.038
Incidental presentation[d]	0.71	0.48-1.06	0.092
Ki67	1.03[a]	1.02-1.04	<.001
Resection status			
R1[e]	1.96	1.01-3.82	.047
RX[f]	1.27	0.83-1.94	.277
Residence in NPCSs[g]	1.89	1.13-3.16	.016

[a]Per unit increase. Reference categories: [b]ENSAT Stage III vs I–II. [c]cortisol ± other hormone secreting tumours vs not–secreting tumours; the category "cortisol secretion" includes tumours secreting cortisol with or without other steroids. [d]Incidental tumours vs symptomatic tumours. [e]R0 vs R1. [f]R0 vs RX. [g] residence in NPCSs vs non–contaminated areas. Valid cases for RFS analysis, $n = 229$.
Abbreviation: HR, hazard ratio.

Table 5 Multivariable analysis of prognostic factors for recurrence-free survival in patients with localized disease, including level of urbanization.

	Recurrence-free survival		
Factor	HR	95% CI	*P* value
Age at diagnosis	1.01[a]	0.99-1.02	.221
ENSAT tumour stage[b]	1.26	0.82-1.92	.292
Cortisol secretion[c]	1.38	0.95-1.99	.088
Incidental presentation[d]	0.63	0.42-0.92	.018
Ki67	1.03[a]	1.02-1.04	<.001
Resection status			
R1[e]	1.96	1.01-3.83	.048
RX[f]	1.23	0.80-1.88	.343
Level of urbanization			
Suburban areas[g]	0.72	0.49-1.07	.103
Rural areas[h]	0.62	0.34-1.12	.110

[a]Per unit increase. Reference categories: [b]ENSAT Stage III vs I-II. [c] Cortisol ± other hormone secreting tumours vs not-secreting tumours; the category "cortisol secretion" includes tumours secreting cortisol with or without other steroids. [d] Incidental tumours vs symptomatic tumours. [e] R0 vs R1. [f] R0 vs RX. [g] Suburban areas vs cities. [h] Rural areas vs cities. Valid cases for RFS analysis, $n = 229$.
Abbreviation: HR, hazard ratio.

rates of recurrence and death in patients with localized disease (stage I-III).

By contrast, no association with survival outcomes emerged when urbanization was used as a proxy for exposure to air pollution, with consistent results across both primary and more parsimonious models. However, these findings should be interpreted cautiously, particularly given the limited number of patients residing in rural areas and the fact that urbanization does not represent a direct measure of environmental exposure.

Table 6 Multivariable analysis of prognostic factors for overall survival in patients with localized disease, including residence in national priority contaminated sites (NPCSs).

	Overall survival		
Factor	HR	95% CI	*P* value
Age at diagnosis	1.03[a]	1.01-1.04	.004
ENSAT tumour stage[b]	1.69	1.08-2.65	.021
Cortisol secretion[c]	1.69	1.11-2.58	.015
Incidental presentation[d]	1.18	0.76-1.83	.453
Ki67	1.03[a]	1.02-1.04	.004
Resection status			
R1[e]	2.49	1.22-5.11	.012
RX[f]	1.20	0.73-1.98	.481
R2[g]	4.74	1.66-13.54	.004
Residence in NPCSs[h]	2.44	1.39-4.28	.002

[a]Per unit increase. Reference categories. [b] ENSAT Stage III vs I-II. [c] Cortisol ± other hormone secreting tumours vs not-secreting tumours; the category "cortisol secretion" includes tumours secreting cortisol with or without other steroids. [d] Incidental tumours vs symptomatic tumours. [e] R0 vs R1. [f] R0 vs RX. [g] R0 vs R2. [h]Residence in NPCSs vs non-contaminated areas.
Abbreviation: HR, hazard ratio.

Table 7 Multivariable analysis of prognostic factors for overall survival in patients with localized disease, including the level of urbanization.

	Overall survival		
Factor	HR	95% CI	*P* value
Age at diagnosis	1.02[a]	1.01-1.04	.006
ENSAT tumour stage[b]	1.69	1.08-2.66	.022
Cortisol secretion[c]	1.59	1.04-2.42	.033
Incidental presentation[d]	.99	.64-1.53	.951
Ki67	1.03[a]	1.02-1.04	<.001
Resection status			
R1[e]	2.74	1.33-5.64	.006
RX[f]	1.24	0.75-2.04	.410
R2[g]	5.08	1.74-14.84	.003
Level of urbanization			
Suburban areas[h]	.64	0.41-1.02	.058
Rural areas[i]	0.82	0.43-1.57	.541

[a]Per unit increase. Reference categories. [b] ENSAT stage III vs I–II. [c] Cortisol ± other hormone secreting tumours vs not-secreting tumours; the category "cortisol secretion" includes tumours secreting cortisol with or without other steroids. [d] Incidental tumours vs symptomatic tumours. [e] R0 vs R1. [f]R0 vs RX. [g] R0 vs R2. [h] Suburban areas vs cities. [i] Rural areas vs cities.
Abbreviation: HR, hazard ratio.

Our findings are partially in contrast with broader oncological data in Italy, where outdoor air pollution has been linked to increased cancer incidence and mortality, especially for lung, breast, and colorectal cancers.[30] Adrenocortical carcinoma is a rare and aggressive malignancy, whose outcomes are highly dependent on a timely diagnosis, expert multidisciplinary management, and surgical treatment in high-volume centres.[31-33] One study[34] demonstrated that early referral to a specialized centre

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improves prognosis, partly due to more timely follow-up and the increased use of adjuvant mitotane treatment. However, these specialized centres are typically located in large urban areas, which may not be easily accessible to patients living in rural or suburban regions. As a result, delays in referral and suboptimal initial management could influence prognosis independently of environmental exposure. These healthcare system–related disparities might have contributed to masking any potential association between level of urbanization and clinical outcomes in our cohort.

Beyond potential differences in healthcare access, the contrasting findings observed for NPCSs and urbanization may also reflect differences in the predominant route and biological relevance of environmental exposure. Airborne pollutants, which are typically more concentrated in densely populated urban areas, have been strongly implicated in the development of several cancers of epithelial origin, including those of the lung, breast, and colon.[14,17,35] By contrast, residence in NPCSs may better capture chronic systemic exposure to lipophilic, persistent organic pollutants or heavy metals absorbed through contaminated water or soil. Such exposures may be particularly relevant for the adrenal cortex because many of these compounds often act as EDCs that preferentially accumulate in steroidogenic tissues. Consistent with this interpretation, *in vitro* studies have shown that bisphenol A (BPA), a well-characterized EDC, directly stimulates adrenal cortical cell proliferation via oestrogen receptor β-mediated activation of the sonic hedgehog signalling pathway.[30]

Our study has several limitations. Firstly, environmental exposure was defined at municipality level and no information was available on duration or intensity of exposure, nor on specific pollutants or proximity to industrial sources. Therefore, residence in NPCSs should be interpreted as an ecological proxy of environmental exposure rather than a direct measure of individual exposure. Consequently, the possibility of ecological fallacy should be considered when interpreting our findings. Similarly, the level of urbanization was used as a contextual proxy and does not capture individual-level exposure to air pollutants or specific pollutant concentrations, as more direct measures were not consistently available across the study period. Therefore, the lack of association observed with urbanization should be interpreted with caution.

Secondly, given the retrospective, observational, multicentre design, residual confounding cannot be excluded. Individual socioeconomic data, systematic germline genetic testing, and detailed diagnostic pathway variables (including symptom-to-diagnosis interval, referral time, and diagnosis-to-surgery interval) were unavailable, preventing a full assessment of potential socioeconomic, hereditary, or healthcare-access influences. Although differences in access to care cannot be completely excluded, they are unlikely to fully explain our findings, as many contaminated sites are located in densely populated areas and close to referral centres, and patients residing in NPCSs originated from geographically diverse municipalities across Italy rather than from isolated or underserved regions. Although follow-up intervals were not fully standardized across centres, ranging from 3 to 6 months, given the similar clinical setting of specialized referral centres, this variability is unlikely to have introduced major systematic bias. Despite the relatively long study period and some imbalance by calendar period, with a higher proportion of excluded patients in earlier years reflecting less complete data collection in historical cohorts, sensitivity analyses accounting for centre and calendar period yielded consistent results, suggesting that these factors did not materially influence the observed associations.

Another limit is that, although residence in contaminated sites and level of urbanization were analysed in separate multivariable models, some geographical overlap is unavoidable and may have influenced the results. Moreover, although our cohort is large for a rare cancer such as ACC, the number of patients residing in contaminated areas was relatively small and analyses were restricted to localized disease because of the limited number of metastatic cases within each environmental subgroup.

Finally, our cohort cannot be considered population-based because cases were assembled from major referral centres in Italy and not captured by cancer registries. Therefore, our data cannot be used to evaluate geographical differences in disease incidence or prevalence.

Despite these potential limitations, our multicentre nationwide study provides evidence that environmental pollutants may be associated with a worse disease course in adult patients with localized ACC. These findings provide a basis for integrating individual-level exposure assessments with molecular tumour profiling to clarify the role of environmental carcinogens in the occurrence and course of ACC.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Conflicts of interest

S.Pu. received a speaker's honorarium from HRA Pharma Rare Diseases (now Esteve) and participated in an advisory board of Recordati Rare Diseases. M.T. has received research grant from HRA Pharma Rare Diseases (now Esteve), and advisory board honoraria from HRA Pharma Rare Diseases (now Esteve) and Recordati Rare Diseases. A.S. received grant support from Recordati Rare Disease. All the other authors declare no competing interests.

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Data availability

We will consider sharing de-identified, individual participant-level data that underlie the results reported in this article on receipt of a detailed request. All requests should be sent to the corresponding author. The corresponding author and lead investigators of this study will discuss all requests and make decisions about whether data sharing is appropriate based on the scientific rigour of the proposal. All applicants will be asked to sign a data access agreement.

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