

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1876318> since 2022-10-12T11:02:02Z

Published version:

DOI:10.1016/S2213-8587(22)00100-0

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Contents page

Supplementary Table 1. Centre-specific patient contribution and ethnicity.

Supplementary Table 2. Clinical characteristics of patients with and without adrenalectomy.

Supplementary Table 3. Multivariate Cox regression analysis of all-cause mortality depending on serum cortisol after the 1 mg dexamethasone-suppression test (with four subgroups).

Supplementary Table 4. Multivariable Cox regression analysis of all-cause mortality depending on serum cortisol after the 1 mg dexamethasone-suppression test and completeness score.

Supplementary Table 5. Cause-specific mortality according to sex and age.

Supplementary Table 6. Cardiovascular events after initial diagnosis of the adrenal incidentaloma.

Supplementary Figure 1. Flow chart of patient selection.

Supplementary Figure 2. Serum cortisol after the 1 mg dexamethasone-suppression test according to age.

Supplementary Figure 3. The functional form of the risk for death associated with different serum cortisol values after the 1 mg dexamethasone-suppression test (adjusted for age and sex).

Study protocol.

Supplementary Table 1. Centre-specific patient contribution and ethnicity.

Centre	Country	All patients (n=3656, 100%)	Ethnicity			Patients also included in EURINE ACT** (n=295, 8.0%)
			Caucasian (n=3521, 96.3%)	Others* (n=75, 2.1%)	Unknown (n=60, 1.6%)	
Bologna	Italy	315	315	0	0	0
Würzburg	Germany	282	282	0	0	29
Mayo	USA	250	220	26	4	23
Stockholm	Sweden	237	208	13	16	0
Athens 1	Greece	225	225	0	0	8
Turin	Italy	225	225	0	0	54
Zagreb	Croatia	197	197	0	0	39
Sheffield	UK	195	194	1	0	0
Rome 1	Italy	168	167	1	0	0
Padua	Italy	167	167	0	0	0
Rome 2	Italy	158	158	0	0	0
Birmingham	UK	151	95	16	40	117
Milan 2	Italy	141	141	0	0	0
Belgrade	Serbia	103	103	0	0	4
Athens 2	Greece	102	102	0	0	0
Thessaloniki	Greece	102	102	0	0	0
Barcelona	Spain	86	74	12	0	0
Milan 1	Italy	84	84	0	0	0
Izmir	Turkey	71	71	0	0	0
St. Petersburg	Russia	59	59	0	0	0
Dresden	Germany	56	56	0	0	6
Ljubljana	Slovenia	54	54	0	0	0
Sofia	Bulgaria	53	53	0	0	0
Oviedo	Spain	50	50	0	0	0
Warsaw	Poland	50	50	0	0	0
Munich	Germany	40	40	0	0	15
NIH	USA	19	13	6	0	0
Zürich	Switzerland	16	16	0	0	0

* Other ethnicities include African, Asian, and South American origin. ** Both the NAPACA Outcome Study and the recently published EURINE ACT Study (Prete et al., Ann Intern Med 2022) were initiated by the European Network for the Study of Adrenal Tumours (ENSAT) consortium and had partly overlapping endpoints. For transparency, we here show the number of patients who participated in both studies.

Abbreviations: NIH, National Institute of Health; UK, United Kingdom; USA, United States of America.

Supplementary Table 2. Clinical characteristics of patients with and without adrenalectomy.

Characteristics	Patients with ADX (n=131)	Patients without ADX (n=3525)	
Demographics			
Women (n, %)	94 (71·8%)	2256 (64·0%)	
Men (n, %)	37 (28·2%)	1269 (36·0%)	
Age, years	54 (47-63)	61 (54-68)	
Follow-up, years	4·7 (3·5-10·2)	7·1 (4·8-10·4)	
Clinical characteristics			
Body mass index, kg/m ²	28·7 (25·6-33·0)	28·1 (25·0-32·3)	
Tumour characteristics			
Left (n, %)	56 (43·1%)	1441 (44·7%)	
Right (n, %)	49 (37·7%)	1044 (32·4%)	
Bilateral (n, %)	25 (19·2%)	739 (22·9%)	
Maximum tumour diameter, mm	30 (23-40)	22 (16-30)	
NAPACA subtype according to serum cortisol after 1 mg DST			
NFA (n, %)	44 (33·6%)	2045 (58·0%)	
PACS (n, %)	65 (49·6%)	1255 (35·6%)	
ACS (n, %)	22 (16·8%)	225 (6·4%)	
Comorbidities			
Hypertension (n, %)	94 (71·7%)	2215 (65·0%)	
Dyslipidaemia (n, %)	58 (44·3%)	1336 (39·8%)	
Diabetes mellitus (n, %)	25 (19·1%)	690 (20·6%)	
CV events before initial diagnosis of the adrenal incidentaloma			
Myocardial infarction and/or coronary intervention (n, %)	5 (3·9%)	194 (6·1%)	
Stroke (n, %)	3 (2·3%)	67 (2·1%)	
Deep vein thrombosis and/or pulmonary embolism (n, %)	1 (0·8%)	61 (1·9%)	
CV events after initial diagnosis of the adrenal incidentaloma			
	Before ADX	After ADX	
Myocardial infarction and/or coronary intervention (n, %)	6 (4·6%)	4 (3·1%)	214 (6·9%)
Stroke (n, %)	3 (2·3%)	2 (1·5%)	107 (3·4%)
Deep vein thrombosis and/or pulmonary embolism (n, %)	2 (1·5%)	2 (1·5%)	89 (2·9%)

Abbreviations: ACS, autonomous cortisol secretion; ADX, adrenalectomy; CV, cardiovascular; DST, dexamethasone suppression test; NFA, non-functioning adenoma; PACS, possible autonomous cortisol secretion.

Supplementary Table 3. Multivariate Cox regression analysis of all-cause mortality depending on serum cortisol after the 1 mg dexamethasone-suppression test (with four subgroups).

Cortisol (nmol/L) after the 1 mg DST	Subjects (n)	Events (n)	HR	95% CI	p
<50	1948	143	1·0		
50-80	766	97	1·29	0·97-1·71	0·085
81-138	440	71	2·00	1·47-2·73	<0·001
>138	225	41	1·78	1·20-2·62	0·004

The analysis was adjusted for hypertension, diabetes mellitus, dyslipidaemia, and former CV events. Patients with missing variables were excluded from the analysis.

Abbreviations: CI, confidence interval; DST, dexamethasone suppression test; HR, hazard ratio.

Supplementary Table 4. Multivariable Cox regression analysis of all-cause mortality depending on cortisol after the 1 mg dexamethasone-suppression test and completeness score.

	Centres with completeness score $\geq 90\%$ (n=21)				Centres with completeness score $< 90\%$ (n=7)			
	Subjects (n)	HR	95% CI	p	Subjects (n)	HR	95% CI	p
NFA	1480	1.00			468	1.00		
PACS	822	1.53	1.16-2.03	0.003	382	1.59	0.95-2.67	0.078
ACS	160	1.90	1.22-2.97	0.005	66	1.59	0.70-3.59	0.265

The analysis was adjusted for hypertension, diabetes mellitus, dyslipidaemia, and former CV events. Centres with vs. without a completeness score of $>90\%$ are separately presented. Patients with missing variables were excluded from the analysis.

Abbreviations: ACS, autonomous cortisol secretion; CI, confidence interval; HR, hazard ratio; NFA, non-functioning adenoma; PACS, possible autonomous cortisol secretion.