Factors associated with the aggressiveness of care at the end of life for patients with cancer dying in hospital: a nationwide retrospective cohort study in mainland Portugal

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ABSTRACT

Introduction There is growing concern about the aggressiveness of cancer care at the end of life (ACCEoL), defined as overly aggressive treatments that compromise the quality of life at its end. Recognising the most affected patients is a cornerstone to improve oncology care. Our aim is to identify factors associated with ACCEoL for patients with cancer dying in hospitals.

Methods All adult patients with cancer who died in public hospitals in mainland Portugal (January 2010 to December 2015), identified from the hospital morbidity database. This database provided individual clinical and demographic data. We obtained hospital and region-level variables from a survey and National Statistics. The primary outcome is a composite ACCEoL measure of 16 indicators. We used multilevel random effects logistic regression modelling ($p<0.05$).

Results We included 92 155 patients: median age 73 years; 62% male; 53% with metastatic disease. ACCEoL prevalence was 71% (95% CI 70% to 71%). The most prevalent indicators were >14 days in the hospital (43%, 42–43) and surgery (28%, 28–28) in the last 30 days. Older age ($p<0.001$), breast cancer (OR 0.83; 95% CI 0.76 to 0.91), and metastatic disease (0.54; 95% CI 0.50 to 0.58) were negatively associated with ACCEoL. In contrast, higher Deyo-Charlson Comorbidity Index ($p<0.001$), gastrointestinal and haematological malignancies ($p<0.001$), and death at cancer centre (1.31; 95% CI 1.01 to 1.72) or hospital with medical oncology department (1.29; 95% CI 1.02 to 1.63) were positively associated with ACCEoL. There was no association between hospital palliative care services at the hospital of death and ACCEoL.

Conclusion Clinical factors related to a better understanding of disease course are associated with ACCEoL reduction. Patients with more comorbidities and gastrointestinal malignancies might represent groups with complex needs, and haematological patients may be at increased risk because of unpredictable prognosis. Improvement of hospital palliative care services could help reduce ACCEoL, particularly in cancer centres and hospitals with medical oncology department, as those services are usually under-resourced, thus reaching few.

Key questions

What is already known about this subject?
- There is growing concern about the aggressiveness of cancer care at the end of life (ACCEoL), defined as overly aggressive treatments that compromise the quality of life.
- The end of life period most studied in relation to ACCEoL is the last month of life, for which Earle *et al*[6] identified key ACCEoL indicators, expanded by Luta *et al.*[12]
- Recognising the most affected patients is a corner-stone to improve this public health unmet need.

What does this study add?
- Unchanged trend of high ACCEoL in a European country (Portugal)—7 out of 10 patients with cancer.
- Most prevalent indicators: >14 days in hospital and surgery in last 30 days of life.
- Older age, breast cancer and metastatic disease were associated with lower ACCEoL.
- Comorbidities, gastrointestinal and haematological cancers with higher ACCEoL.

How might this impact on clinical practice?
- Clinicians should consider cancer type, disease stage, comorbidities, age and the influence of hospital oncology culture, to help patients with cancer to avoid ACCEoL.

INTRODUCTION

Towards the end of life (EoL), patients with cancer wish to feel comfortable, be treated with dignity and achieve a sense of completion.[1] They also wish to avoid overly aggressive treatments, which can compromise symptom control and advance care planning.[2] Appropriate management of EoL care has been raised as a quality-of-care issue and indicators have been developed to identify health systems that apply overly intensive treatments

for terminal advanced cancer patients with very limited clinical benefit, defined as aggressiveness of cancer care at the EoL (ACCEoL).[3] As one component of EoL, the ACCEoL is interconnected with deleterious effects for patients and families such as worse quality of life and bereavement outcomes.[4 5] This led to growing concern across societies about the ACCEoL.[6–11]

Earle et al[6] reported one of the first ACCEoL studies, based on administrative data measuring key indicators within the last month of life, including overuse of chemotherapy (new regimen within 30 days, or any administration within 14 days before death), underuse of hospice care, and high rates of emergency room visits, hospitalisation or intensive care unit (ICU) admissions. They found that each indicator was present in less than one-third of patients but also that ACCEoL prevalence was increasing in the 90s in the USA.[6] Studies followed in other countries, interestingly with different findings.[7–11] Luta et al[12] proposed an expanded list of ACCEoL measures based on a systematic review.

Despite these advances in ACCEoL research, the issue remains neglected yet vital for clinical oncology, in face of the growing number of people dying with cancer.[13] Despite two-thirds of the population express a preference to die at home in a scenario of advanced cancer[14] and increases in several nations on the percentage of cancer patients dying at home rather than in hospital,[15] still many patients remain increasingly exposed to other ACCEoL indicators, such as ICU admission.[16] The rise of hospital deaths in other countries suggests a level of dependency on hospital resources and of ACCEoL which are contrary to people's preferences.[14 17–19]

Recognising the profile of patients at risk of receiving ACCEoL is critical for better understanding this public health unmet need and improving oncology care. Our study aims to identify factors associated with ACCEoL for cancer patients dying in hospitals.

METHODS
Study design and setting
This is a nationwide retrospective cohort study of adults who died with cancer in Portuguese hospitals. The study followed the REporting of studies Conducted using Observational Routinely-collected health Data statement.[20]

Patients
We included all patients that: (1) died in a public hospital in mainland Portugal between January 2010 and December 2015; (2) were aged ≥18 years at the time of death and (3) had a diagnosis of cancer recorded in the episode leading to death, using International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM) codes from the chapter 'neoplasms' (codes 140–239), excluding benign neoplasms, carcinoma in situ, neoplasms of uncertain behaviour or unspecified nature (210-239).

Primary outcome
Study outcome is a composite binary measure of ACCEoL, positive in the presence of at least one of 16 individual indicators (S1 - online supplemental file 1). The list of indicators from Earle et al[6] was expanded based on the systematic review by Luta et al.[12] A national expert panel assessed content validity. For all patients, all indicators were measured for the last 30 days of life, except the use of chemotherapy and immunotherapy/biological agents, which was shortened to the last 14 days of life, following Earle et al's criteria.[6]

Data sources
We used the hospital morbidity database (HMD) to identify patients and obtain individual-level data. The HMD contains routinely-collected data from all public hospitals in mainland Portugal for funding purposes, since 1989.[21] The dataset was anonymised by the Portuguese Health System Central Administration and included: (1) demographic data: sex, age at death and borough of residence; (2) clinical data coded by ICD-9-CM: metastatic disease status, procedures and main or secondary diagnoses used for the calculation of the Deyo-Charlson Comorbidity Index (DCCI)— used to predict mortality that derives from the sum of the score attributed to each comorbidity out of 17 chronic medical conditions[22 23] and (3) administrative data: date of admission, discharge or death, type of treatment (medical vs surgical) and hospital of death.

In September 2016, we surveyed all hospital administration boards and directors of palliative care services (PCS) created before January 2016. Following recommendations from a Cochrane Review on methods to increase response to postal and electronic questionnaires,[24] we obtained a 78% response rate. We used a semistructured questionnaire to obtain the following information: (1) hospital: hospital type (general vs cancer centre), hospital dimension (number of beds), existence of medical oncology department (MOD); (2) PCS: existence and creation date, existence of palliative care unit and number of beds. We made follow-up contacts and consulted the national directory of PCS to complete missing data. Hospital-level data were linked to individual-level data by hospital of death variable from HMD.

We obtained lists of boroughs classified by health region, urbanisation level (predominantly urban, midurban, predominantly rural) based on Census 2011 data and by deprivation level based on Census 2001 data (European Deprivation Index).[25] Region-level data were linked to individual and hospital-level data by borough of residence variable from HMD.

Statistical analysis
We first described the study population, comparing the characteristics of patients who received ACCEoL with those that did not, using Pearson's χ^2 or Mann-Whitney tests. We then determined the prevalence of the composite measure of ACCEoL and each individual indicator for the whole population and by metastatic disease

status, primary cancer site and type of hospital of death. We examined trends in composite and individual indicators from 2010 to 2015, using χ^2 test for trend. We considered a difference of >5% as clinically meaningful.

Taking the composite ACCEoL measure as the dependent variable, unadjusted odds ratio (ORs) with 95% confidence interval (CI) were calculated for each independent variable. We used multilevel random effects logistic regression modelling (accounting for individual, hospital and region levels), including year of death and all independent variables that showed association with ACCEoL on unadjusted analysis. Finally, we conducted a subgroup analysis for patients with metastatic disease. All analyses were based on complete cases using STATA. IC12.1 (p<0·05).

RESULTS
Patient characteristics
We included 92 155 patients (S2 - online supplemental file 1), 62% male and median age of 73 years (interquartile range - IQR, 62–81). Fifty-three percent had metastatic disease and the most common primary solid tumour sites were lung (16%) and colorectal (10%). Twelve percent had haematological malignancies. The median DCCI score was eight points (IQR, 4–9). Only 15% died in a cancer centre but nearly all patients died in a hospital with MOD (93%). Most (66%) died in a hospital with hospital PCS (hPCS). The characteristics of the groups with and without ACCEoL were statistically different at: i) individual-level: all variables except year of death; ii) hospital-level: hPCS, MOD, hospital type, hospital dimension, health region; and iii) region-level: palliative care unit beds/100 deaths-year (table 1).

PCS resources
Survey results showed that the percentage of hospital centres with hPCS increased from 42% (13/31) in 2010 to 74% (23/31) in 2015 (p<0·05), reflected in an increase of the percentage of patients who died in hospitals with hPCS (50% in 2010 to 82% in 2015, p<0·001) (S3 - online supplemental file 1).

ACCEoL prevalence
The prevalence of the composite ACCEoL measure was 71% (95% CI 70% to 71%). The difference by metastatic disease status was only 3% (patients with metastatic disease: 70% vs others: 73%). ACCEoL also varied by primary cancer site (63% in breast cancer to 79% in haematological malignancies) and type of hospital of death (74% in cancer centre vs 69% in general hospital) (S4 - online supplemental file 1).

The most prevalent indicators were >14 days of length of stay in hospital (43%, 95% CI 42 to 43) and surgery (28%, 95% CI 28 to 28) within the last 30 days, with no clinically meaningful differences between patients with versus without metastatic disease except for ICU admission (4% vs 10%, respectively), mechanical ventilation

(2% vs 8%) and insertion of endotracheal tube (15% vs 22%) (figure 1).

The primary outcome remained stable overtime (from 71% in 2010 to 72% in 2011) and despite some indicators showing statistically significant changes from 2010 to 2015, none were considered clinically meaningful (S5 - online supplemental file 1).

Factors associated with ACCEoL
In multivariate analysis, older age (p<0·001), breast cancer (OR 0·83; 95% CI 0·76 to 0·91), and metastatic disease (OR 0·54; 95% CI 0·50 to 0·58) were negatively associated with ACCEoL. In contrast, higher DCCI (p<0·001), gastrointestinal and haematological malignancies (p<0·001), and death at a cancer centre (OR 1·31; 95% CI 1·01 to 1·72) or at a hospital with MOD (OR 1·29; 95% CI 1·02 to 1·63) were positively associated with ACCEoL. Adjusting for confounders, there was no association between existence of hPCS and ACCEoL. There was a contextual effect of hospital-level with a median OR of 1·20 (95% CI 1·15 to 1·27), but no effect of region (S6 - online supplemental file 1). The subgroup analysis of patients with metastatic disease showed also a negative association with ACCEoL for male sex (OR 0·93, 95% CI 0·88 to 0·98) and cancer as main diagnosis of last hospital admission (OR 0·88, 95% CI 0·83 to 0·94), and a positive association for year of death (OR 1·03, 95% CI 1·01 to 1·05) (table 2).

DISCUSSION
Our study showed an unchanged trend of high prevalence of ACCEoL in a European country. Seven out of 10 adult cancer patients dying in Portuguese public hospitals between 2010 and 2015 received ACCEoL, more than in other Western countries (71% vs 22%–65%).[6 7 10 26]

The high rate of hospitalisation may reflect not only the intensity of clinical care, but also the extent of social and clinical support in community and home settings. Free access to the National Health Service for cancer patients facilitates hospitalisation in a context of scarce community support. This should be considered when establishing comparisons with different health systems, where the prevalence of the most common individual indicator of our study, >14 days in hospital within the last month of life, was lower (43% vs 11%–30%).[6 9] On the other hand, we found ICU admission prevalence at the bottom of the previously reported range (6% vs 3%–25%)[5–9] and less prevalent in patients with metastatic disease (4% vs 10%), suggesting that the reduced use of limited and merely clinically driven hospital resources may reflect an adequate intensity of clinical care, despite the high rate of ACCEoL mainly due to hospitalisation.

However, more than one-fourth of the patients were submitted to a surgical intervention at the EoL, the most common procedure and the second most prevalent individual indicator. Although palliative surgical interventions in advanced stages and complications from a

Table 1 Patients characteristics

|	Characteristics		All patients (n=92 155)	Patients who died with ACCEoL (n=65 564)	Patients who died without ACCEoL (n=26 591)	Tests (χ^2/Mann-Whitney (M-W))
Patient and health condition	**Sex** (% male)		61.9	62.2	61.2	χ^2 p=0.004
	Age at death	Median in years (IQR)	73 (62–81)	72 (61–80)	75 (65–83)	M-W p<0.001
		18–39 (%)	2.0	2.3	1.1	M-W p<0.001
		40–49 (%)	5.2	5.7	4.0	
		50–59 (%)	13.1	13.9	11.1	
		60–69 (%)	21.4	22.5	18.7	
		70–79 (%)	29.5	29.8	28.6	
		80–89 (%)	24.7	22.5	29.9	
		≥90 (%)	4.3	3.3	6.6	
	Primary cancer type	Lung (%)	15.9	14.4	16.5	χ^2 p<0.001
		Colorectal (%)	10.2	9.5	8.6	
		Gastric (%)	8.7	8.5	6.7	
		Prostate (%)	8.5	6.7	9.8	
		Breast (%)	5.8	4.7	7.1	
		Haematological (%)	11.9	12.4	8.0	
		Other (%)	41.3	43.7	43.4	
	Deyo-Charlson Comorbidity Index, median score (IQR)		8 (4–9)	8 (4–9)	8 (4–9)	M-W NS
		Less than mild: 2 (%)	11.6	10.4	14.3	M-W p<0.001
		Mild: 3–4 (%)	16.1	15.9	16.7	
		Moderate: 5–6 (%)	8.2	8.8	6.9	
		Severe:>6 (%)	64.1	64.9	62.1	
	Cancer as main diagnosis of last hospital admission (%)		65.9	66.8	63.6	χ^2 p<0.001
	Metastatic disease (%)		53.0	52.1	55.4	χ^2 p<0.001
	Year of death (%)	2010	16.0	15.9	16.1	M-W NS
		2011	16.4	16.5	16.2	
		2012	16.4	16.4	16.3	
		2013	16.8	16.9	16.7	
		2014	17.0	17.0	17.1	
		2015	17.4	17.3	17.5	

Continued

Table 1 Continued

	Characteristics	All patients (n=92 155)	Patients who died with ACCEoL (n=65 564)	Patients who died without ACCEoL (n=26 591)	Tests (χ^2/Mann-Whitney (M-W))
Hospital where patient died	**Hospital palliative care service** (% yes)	65.8	67.2	62.5	χ^2p<0.001
	Median years of existence (IQR)	4.6 (2.3–8.6)	4.6 (2.4–8.4)	4.6 (2.2–9.0)	M-W NS
	Quartile 1 (0.003–2.3 years) (%)	16.5	16.5	16.5	χ^2p<0.001
	Quartile 2 (2.3–4.6 years) (%)	16.4	17.1	14.8	
	Quartile 3 (4.6–8.6 years) (%)	16.5	17.0	15.2	
	Quartile 4 (8.6–23.0 years) (%)	16.4	16.7	15.9	
	Medical oncology department (% yes)	92.9	93.5	91.6	χ^2p<0.001
	Hospital type (% cancer centre)	14.7	15.2	13.4	χ^2p<0.001
	Hospital dimension, median no. beds (IQR)	380 (319–568)	380 (319–570)	380 (319–565)	M-W p=0.011
	Quartile 1 (6–319 beds) (%)	29.7	30.3	28.3	M-W p<0.001
	Quartile 2 (320–380 beds) (%)	21.0	20.2	22.8	
	Quartile 3 (381–568 beds) (%)	24.5	23.6	26.5	
	Quartile 4 (568–1299 beds) (%)	24.8	25.8	22.4	
	Health region (HR) Lisbon and Tagus Valley (%)	40.8	41.4	39.4	χ^2p<0.001
	North (%)	31.4	30.5	33.8	
	Centre (%)	19.1	19.7	17.7	
	Alentejo and Algarve (%)	8.6	8.4	9.2	
Region where patient lived	**Palliative care unit beds,** median no of palliative care unit beds/100 deaths-year, per HR (IQR)	1.00 (0.81–1.22)	1.00 (0.81–1.22)	1.00 (0.80–1.22)	M-W NS
	Quartile 1 (0–0.8) (%)	29.8	29.5	30.4	χ^2p<0.001
	Quartile 2 (0.8–1.0) (%)	22.4	22.2	23.2	
	Quartile 3 (1.0–1.2) (%)	23.5	24.1	22.1	
	Quartile 4 (1.2–19.4) (%)	24.3	24.2	24.4	
	Home palliative care services (% yes)	11.6	11.5	11.8	NS
	Median years of existence (IQR)	5.3 (2.3–15.8)	5.5 (2.3–15.8)	4.9 (2.2–15.6)	NS
	Quartile 1 (0.003–2.3 years) (%)	2.9	2.8	3.0	NS
	Quartile 2 (2.3–5.4 years) (%)	2.9	2.8	3.0	
	Quartile 3 (5.4–15.9 years) (%)	2.9	2.9	2.9	
	Quartile 4 (15.9–59.8 years) (%)	2.9	3.0	2.7	
	European Deprivation Index, median score (IQR)	−1.24 (−2.34-(−0.01))	−1.24 (−2.34–0.00)	−1.24 (−2.34-(−0.02))	NS
	Quartile 1 (least deprived: −7.31 to −2.34) (%)	25.5	25.6	25.2	NS
	Quartile 2 (-2.34 to −1.24) (%)	24.5	24.5	24.6	
	Quartile 3 (-1.24 to −0.01) (%)	25.0	24.8	25.4	
	Quartile 4 (most deprived: −0.01 to 13.47) (%)	25.0	25.1	24.8	
	Urbanisation level Predominantly urban (%)	69.0	69.0	68.8	NS
	Mid-urban (%)	15.2	15.0	15.6	
	Predominantly rural (%)	15.8	15.9	15.6	

ACCEoL, aggressiveness of cancer care at the end of life; NS, non-significant.
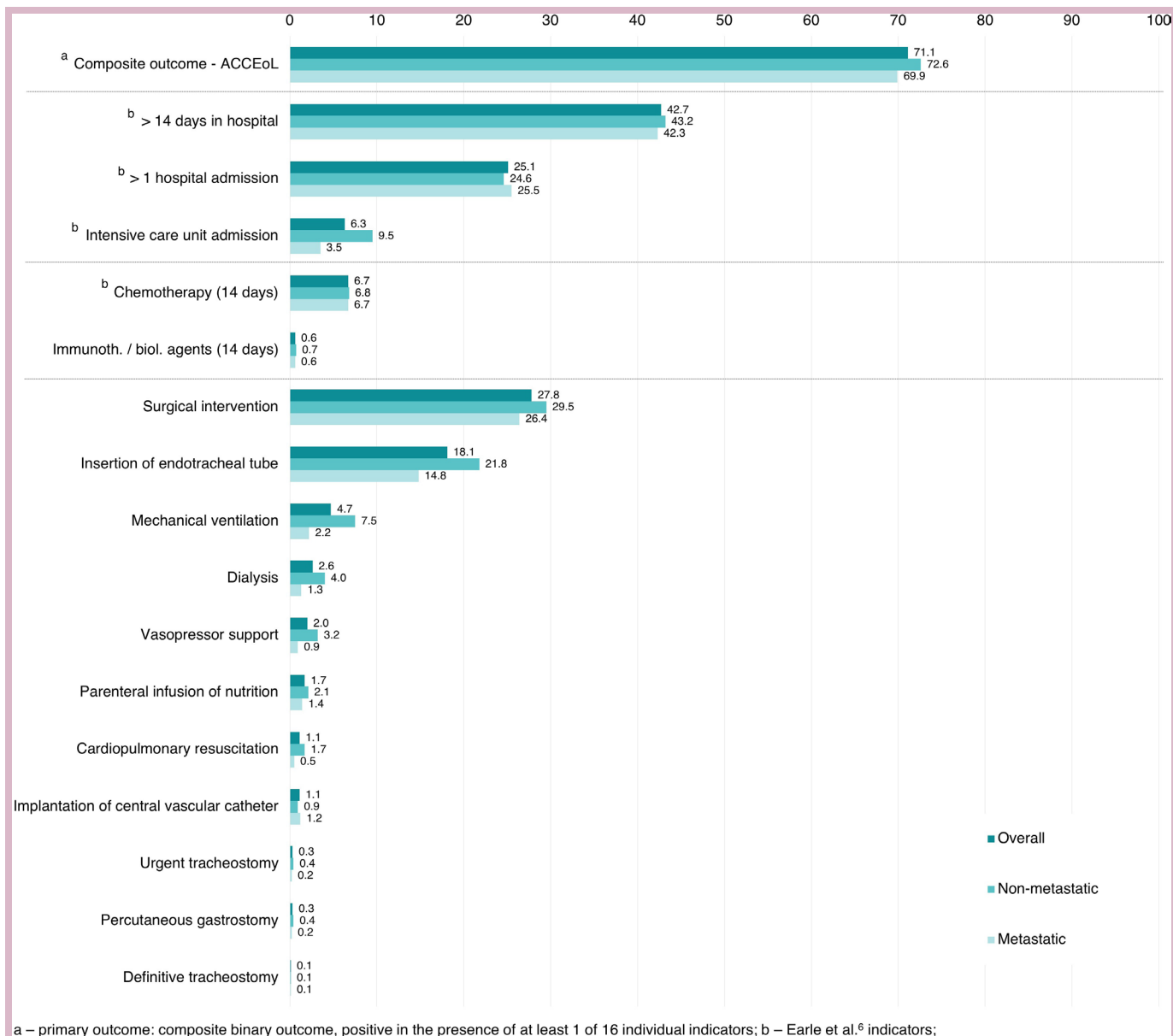
Figure 1 Prevalence of composite and individual indicators of ACCEoL (%), overall and by disease stage. ACCEoL, aggressiveness of cancer care at the end of life; Immunoth, Immunotherapy; Biol, biological.

primary tumour resection procedure with curative intent might be causes, further studies should focus on this individual outcome. We found a relatively low prevalence of chemotherapy administration in the last 14 days of life, compared with previous reports (7% vs 2%–24%).[6–9] However, this indicator might be underestimated since it did not measure the administration of oral agents.

Breast cancer was the primary cancer type associated with the lowest rate of ACCEoL, probably due to better knowledge of clinical trajectories of disease subtypes. On the other hand, we found that patients with gastrointestinal and haematological malignancies are at increased risk of ACCEoL. In patients with gastrointestinal malignancies, it may be due to higher rate of postoperative complications in early stages and digestive haemorrhage or malignant obstructions in late stages.[26] Patients with

haematological malignancies represent a subgroup with more unpredictable prognosis and higher percentage of curative intent treatments, and therefore, as previously reported,[7 10] associated with higher ACCEoL. Also as previously reported,[6 7] patients with higher DCCI were at increased risk of ACCEoL, certainly related with higher complexity of care. As expected, patients with metastatic disease were less likely to experience ACCEoL, mainly when cancer was the main diagnosis of last hospital admission, suggesting that hospitalisation due to late stage disease progression is recognised. Despite trends remaining unchanged in the overall sample, ACCEoL is increasing over time in metastatic disease. This might be explained by the scientific advances on systemic antineoplastic treatments, mostly experienced in advanced stages. Aligned with literature,[7 9] age was the most influential

Table 2 Factors associated with ACCEoL: multilevel logistic regression model

	Factors	Unadjusted			Adjusted (n=57 683)		Adjusted (subgroup of patients with metastatic disease) (n=31 199)	
		N	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Patient and health condition	**Sex** (female—reference)	92 155						
	Male	57 071	1.04 (1.01 to 1.08)	<0.01	0.97 (0.93 to 1.01)	0.12	0.93 (0.88 to 0.98)	0.01
	Age at death (in years)	92 155						
	18–39	1 800	Reference	<0.001	Reference	<0.001	Reference	<0.001
	40–49	4 790	0.71 (0.61 to 0.81)		0.81 (0.68 to 0.97)		0.78 (0.62 to 0.97)	
	50–59	12 038	0.61 (0.54 to 0.70)		0.70 (0.59 to 0.82)		0.65 (0.53 to 0.80)	
	60–69	19 745	0.59 (0.52 to 0.67)		0.65 (0.55 to 0.76)		0.57 (0.47 to 0.70)	
	70–79	27 147	0.51 (0.45 to 0.58)		0.54 (0.46 to 0.63)		0.48 (0.39 to 0.59)	
	80–89	22 718	0.37 (0.33 to 0.42)		0.40 (0.34 to 0.46)		0.36 (0.29 to 0.44)	
	≥90	3 917	0.25 (0.22 to 0.28)		0.27 (0.23 to 0.32)		0.23 (0.18 to 0.30)	
	Primary cancer type	92 155						
	Lung	14 695	Reference	<0.001	Reference	<0.001	Reference	<0.001
	Colorectal	9 419	1.27 (1.19 to 1.34)		1.55 (1.44 to 1.67)		1.17 (1.07 to 1.28)	
	Gastric	8 024	1.45 (1.36 to 1.54)		1.73 (1.60 to 1.87)		1.47 (1.33 to 1.62)	
	Prostate	7 825	0.81 (0.77 to 0.86)		1.04 (0.97 to 1.13)		1.08 (0.97 to 1.20)	
	Breast	5 346	0.77 (0.72 to 0.82)		0.83 (0.76 to 0.91)		0.72 (0.65 to 0.80)	
	Haematological	11 013	1.77 (1.67 to 1.88)		1.73 (1.60 to 1.87)		·	
	Other	38 046	1.13 (1.08 to 1.17)		1.29 (1.23 to 1.36)		1.12 (1.04 to 1.20)	
	Deyo-Charlson Comorbidity Index	92 155						
	Less mild: 2	10 646	Reference	<0.001	Reference	<0.001	·	·
	Mild: 3–4	14 864	1.31 (1.24 to 1.38)		1.31 (1.22 to 1.40)		·	
	Moderate: 5–6	7 590	1.73 (1.62 to 1.84)		1.68 (1.54 to 1.84)		·	
	Severe:>6	59 055	1.43 (1.37 to 1.49)		2.20 (2.02 to 2.38)		·	
	Cancer as main diagnosis of last hospital admission (no—reference)	92 155						
	Yes	60 732	1.15 (1.12 to 1.19)	<0.001	1.04 (0.99 to 1.08)	0.10	0.88 (0.83 to 0.94)	<0.001
	Metastatic disease (no—reference)	92 155						
	Yes	48 870	0.88 (0.85 to 0.90)	<0.001	0.54 (0.51 to 0.58)	<0.001	·	·
	Year of death (continuous)	92 155	1.00 (0.99 to 1.01)	0.71	1.01 (1.00 to 1.03)	0.13	1.03 (1.01 to 1.05)	0.01

Continued

Table 2 Continued

	Factors	N	Unadjusted		Adjusted (n=57 683)		Adjusted (subgroup of patients with metastatic disease) (n=31 199)	
			OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Hospital where patient died	**Hospital palliative care service**	67 262						
	No existence	23 001	Reference	<0.001	Reference	0.18	Reference	0.42
	0.003–2.3 years of existence	11 075	1.15 (1.09 to 1.20)		1.02 (0.94 to 1.11)		1.02 (0.92 to 1.13)	
	2.3–4.6 years of existence	11 038	1.32 (1.26 to 1.39)		1.10 (1.00 to 1.22)		1.09 (0.96 to 1.23)	
	4.6–8.6 years of existence	11 076	1.28 (1.22 to 1.34)		1.05 (0.92 to 1.18)		1.02 (0.87 to 1.18)	
	8.6–23.0 years of existence	11 063	1.20 (1.14 to 1.26)		0.97 (0.79 to 1.20)		1.01 (0.79 to 1.30)	
	Medical Oncology Department (no—reference)	62 465						
	Yes	58 055	1.31 (1.23 to 1.40)	<0.001	1.29 (1.02 to 1.63)	0.03	1.26 (0.98 to 1.62)	0.07
	Hospital type (General hospital—reference)	92 155						
	Cancer centre	13 536	1.16 (1.12 to 1.21)	<0.001	1.31 (1.01 to 1.72)	0.04	1.38 (1.04 to 1.83)	0.03
	Hospital dimension	57 683						
	6–319 beds	17 156	Reference	<0.001	Reference	0.20	Reference	0.10
	320–380 beds	12 104	0.83 (0.79 to 0.87)		1.11 (1.00 to 1.24)		1.12 (0.99 to 1.28)	
	381–568 beds	14 123	0.83 (0.79 to 0.87)		1.08 (0.96 to 1.24)		1.14 (0.98 to 1.32)	
	568–1299 beds	14 300	1.08 (1.03 to 1.13)		1.03 (0.88 to 1.21)		1.10 (0.91 to 1.33)	
Region where patient lived	**Palliative care unit beds***	92 155						
	0–0.8 beds/100 deaths, per HR	27 427	Reference	<0.01	Reference	0.24	Reference	0.13
	0.8–1.0 beds/100 deaths, per HR	20 687	0.96 (0.91 to 1.00)		0.97 (0.92 to 1.02)		0.95 (0.88 to 1.02)	
	1.0–1.2 beds/100 deaths, per HR	21 675	1.13 (1.08 to 1.18)		1.05 (0.97 to 1.12)		1.10 (1.00 to 1.21)	
	1.2–19.4 beds/100 deaths, per HR	22 366	0.98 (0.94 to 1.02)		0.96 (0.88 to 1.04)		0.94 (0.84 to 1.05)	
	Home palliative care team	92 155						
	No existence	81 438	Reference	0.06	·	·	·	·
	0.003–2.3 years of existence	2 662	0.93 (0.85 to 1.01)		·		·	
	2.3–5.4 years of existence	2 663	0.92 (0.85 to 1.00)		·		·	
	5.4–15.9 years of existence	2 662	1.00 (0.91 to 1.08)		·		·	
	15.9–59.8 years of existence	2 660	1.07 (0.98 to 1.17)		·		·	
	European Deprivation Index	85 688						
	least deprived: −7.31 to −2.34	21 830	Reference	0.41	·	·	·	·
	−2.34 to −1.24	21 024	0.98 (0.94 to 1.02)		·		·	
	−1.24 to −0.01	21 415	0.96 (0.92 to 1.00)		·		·	
	most deprived: −0.01 to 13.47	21 419	1.00 (0.95 to 1.04)		·		·	
	Urbanisation level	85 790						
	Predominantly urban	59 170	Reference	0.32	·	·	·	·
	Mid-urban	13 033	0.96 (0.92 to 1.00)		·		·	
	Predominantly rural	13 587	1.02 (0.97 to 1.06)		·		·	

*Median number of palliative care unit beds/100 deaths-year, per health region.
ACCEoL, aggressiveness of cancer care at the end of life; HR, health region.

factor on ACCEoL, with the oldest patients having 73% lower odds of receiving ACCEoL compared with the youngest. Male sex in metastatic patients was associated with decreased risk of ACCEoL, a disparity not clearly understood and the opposite of the reported in other continents,[7 27] maybe resulting from cultural differences.

Considering environmental factors, death at a cancer centre and death at a hospital with MOD were associated

with higher risk of receiving ACCEoL. These findings might be due to higher complexity of cases treated in cancer centres or easier access to antineoplastic treatments and clinical trials when MOD exists at the hospital of admission. On the other hand, and in contrast with what literature reports,[28] our study showed no association of availability of hPCS and reduction of ACCEoL. This result might be influenced by the fact that hospitals with hPCS are often those with a case mix of more complex patients, with higher risk of ACCEoL. It also may be because hPCS effect was measured at a hospital-level, since the HMD did not provide individual data on hPCS intervention (we could only measure the existence of hPCS at the hospital where a given patient died). Moreover, late referral or limited human resources in hPCS could hinder their impact on ACCEoL. There was no effect of region-level characteristics on ACCEoL, as opposed to other studies.[7]

This is a robust nationwide study that used multivariate methods to control for confounders at different levels. However, the use of routinely-collected data generated for administrative purposes does not allow to conclude to what extent the ACCEoL was adequate or inadequate for each individual, as the HMD does not contain the cause of death or the setting of the anticancer treatment (curative vs palliative). To overcome this limitation, we planned the subgroup analysis of metastatic disease as a sensitivity analysis, since the treatment intent in these patients is mostly palliative. We expanded the Earle *et al*'s framework,[6] but emergency department visits were not included in this study, thus the prevalence of ACCEoL could be even higher than we estimated (measurement bias). In contrast, the study was restricted to people who died in hospital, who are likely to receive higher ACCEoL than those who died elsewhere (selection bias).

CONCLUSIONS

This study unravelled important data on ACCEoL and associated risk factors, expanding the earlier framework for measuring ACCEoL. We confirmed that clinical factors related with a better understanding of disease course are associated with ACCEoL reduction. In contrast, we identified groups of patients at increased risk for ACCEoL such as patients with more comorbidities, gastrointestinal and haematological malignancies. Therefore, clinicians should seek for better integration of prognostic estimations with adequate timing for anticipated discussion of patients and families' preferences and expectations, particularly within the high-risk groups identified by our study. Efforts should be made for empowerment and reinforcement of the growing number of hospital and home PCS, with human resources, earlier referral and integration into a comprehensive cancer care plan, mainly in cancer centres and hospitals with MOD. The study recognised need for further research on the impact of the social and clinical community support on hospitalisation rates, determinants for surgery procedure, management of haematological malignancies at the EoL, and higher ACCEoL in patients who deceased at cancer centres or hospitals with MOD.

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of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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