Lung Cancer 157 (2021) 109–115

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Lung cancer patients with COVID-19 in Spain: GRAVID study

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ARTICLE INFO

Keywords:
COVID-19
Lung cancer
Mortality
Anticancer therapy
Prognosis

ABSTRACT

Introduction: Patients with cancer may be at increased risk of more severe COVID-19 disease; however, prognostic factors are not yet clearly identified. The GRAVID study aimed to describe clinical characteristics, outcomes, and predictors of poor outcome in patients with lung cancer and COVID-19.

Methods: Prospective observational study that included medical records of patients with lung cancer and PCR-confirmed COVID-19 diagnosis across 65 Spanish hospitals. The primary endpoint was all-cause mortality; secondary endpoints were hospitalization and admission to intensive care units (ICU).

Results: A total of 447 patients with a mean age of 67.1 ± 9.8 years were analysed. The majority were men (74.3 %) and current/former smokers (85.7 %). NSCLC was the most frequent type of cancer (84.5 %), mainly as adenocarcinoma (51.0 %), and stage III metastatic or unresectable disease (79.2 %). Nearly 60 % of patients were receiving anticancer treatment, mostly first-line chemotherapy. Overall, 350 (78.3 %) patients were hospitalized for a mean of 13.4 ± 11.4 days, 9 (2.0 %) were admitted to ICU and 146 (32.7 %) died. Advanced disease and the

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https://doi.org/10.1016/j.lungcan.2021.05.014
Received 16 April 2021; Received in revised form 5 May 2021; Accepted 10 May 2021
Available online 14 May 2021
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use of corticosteroids to treat COVID-19 during hospitalization were predictors of mortality. Hospitalized, non-end-of-life stage patients with lymphocytopenia and high LDH had an increased risk of death. Severity of COVID-19 correlated to higher mortality, ICU admission, and mechanical ventilation rates.
Conclusions: Mortality rate was higher among patients treated with corticosteroids during hospitalization, while anticancer therapy was not associated with an increased risk of hospitalization or death. Tailored approaches are warranted to ensure effective cancer management while minimizing the risk of exposure to SARS-CoV-2.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a major health emergency worldwide. Significant morbidity and mortality rates have been reported across countries since February 2020, with more than 79.5 million confirmed COVID-19 cases and 1.7 million deaths worldwide at the time of writing. Spain has been strongly hit by the pandemic, resulting in the saturation of the national healthcare system. To date, the number of reported cases in Spain exceeds 1.8 million, of which 208 626 cases required hospitalization, 18 004 were admitted to intensive care units (ICU), and 50 122 died [1].

Patients with lung cancer may be more susceptible to infection by SARS-CoV-2 than non-cancer patients due to the systemic immunosuppression caused either by the tumour itself or the anticancer treatments. [2] Several studies have attempted to identify prognostic factors that could help in risk stratification and clinical management [3–7]. Smoking has proven to be a risk factor for progression of COVID-19 in the general population [8], while advanced age and prior heart disease are factors for poor prognosis. [9] Nonetheless, the risk of complications in patients with cancer seems to vary depending on the type of tumour, with an increased risk of death in patients with lung cancer and haematological malignancies [4,6,10].

Whether to start, continue or withhold systemic anticancer treatments has challenged physicians who manage patients with cancer and COVID-19. Early reports from China suggested that the administration of chemotherapy was associated with a more severe COVID-19 course. [11] Besides, immunotherapy has been associated with worse outcomes [7]. Recent evidence in larger cohorts suggests that systemic anticancer therapies do not increase the incidence of severe events or the risk of death in patients with lung cancer [4,12]. Numerous expert-based recommendations are being published to guide healthcare professionals in cancer care [13–17]. Furthermore, the growing number of prospective studies [3–5,18] and meta-analyses [19,20] will assist in the characterization of susceptible patients according to their cancer features, to eventually minimize COVID-19 burden among this population.

In this context, the LunG canceR pAtients coVid19 Disease (GRAVID) study aimed to describe the clinical characteristics and outcomes of patients with lung cancer who were affected by COVID-19 in Spain, addressing mortality, hospitalization and ICU admission rates, along with potential predictors for poor prognosis.

2. Methods

2.1. Study design and participants

This prospective study included medical history data from patients with cancer who developed COVID-19 and were registered at 65 Spanish hospitals since April 24th, 2020 Data cut-off for this report was July 3rd, 2020.

Individual data of patients with lung cancer were prospectively collected following a confirmed COVID-19 diagnosis by PCR. Inclusion was limited only by the identification of cases and their electronic medical records. Patient demographics and clinical characteristics, including cancer diagnosis and treatments, were collected.

2.2. Ethical approval

The study was registered in the ClinicalTrials.gov database (NCT04344002). This registry meets all the requirements for exemption of consent according to the "International Ethical Guidelines for Health-related Research Involving Humans" (CIOMS-OMS 2016). The processing of patients' personal and health data without consent for use is covered by Article 9.2(h) and (j) of Regulation (EU) 2016/679, and complied with the criteria set out in Data Protection Act 3/2018, specifically paragraph 2(b), (d), (e), (f), and (g) of DA 17.

2.3. Outcomes

The primary outcome was to assess all-cause mortality. Variables for analysis included: sex, age, comorbidities, type of tumour, histology, end-of-life stage, disease status, mutations, stage at diagnosis of tumour, stage at diagnosis of COVID-19 infection, anticancer treatments, treatment line, pharmacological treatments, and clinical laboratory parameters. Secondary endpoints were hospitalization, admission to intensive care units (ICU), and duration of hospitalization.

COVID-19 disease was categorized as severe in patients who met at least one of the following criteria: hypoxemia (oxygen saturation < 93 %), tachypnoea (respiratory rate > 30 breaths per minute), and/or respiratory failure (oxygen in arterial blood [PaO2]/fraction of oxygen in inspired air [FiO2] ratio < 300).

2.4. Statistical analysis

A descriptive analysis of study variables was performed. Quantitative variables are presented as mean, standard deviation (SD), median, and interquartile range (IQR). Qualitative variables are described as frequencies and percentages.

Univariate logistic models were used to assess the association between demographic and clinical characteristics and outcomes. Multivariate logistic regression was used to estimate odd ratios and 95 % confidence intervals (CI) for each factor. Variables for the multivariate analysis were selected considering factors known to be associated with COVID-19 outcomes in the general population. Goodness of fit was verified using the Hosmer-Lemeshow test. The R Foundation for Statistical Computing version 3.6.1 (Vienna, Austria) was used for data processing and visualisation.

3. Results

3.1. Patient characteristics

In total, 447 patients with lung cancer and COVID-19 diagnosis were included for analysis. Baseline demographics and clinical characteristics are shown in Table 1 and Supplementary Table 1. With a mean (SD) age of 67.1 (9.8) years, most patients were men (74.3 %), older than 60 years of age (78.3 %), and current (24.8 %) or former (60.9 %) smokers. Non-small cell lung cancer (NSCLC) was the most frequent type of cancer (84.5 %) and 51 % of patients had adenocarcinoma. Most patients were diagnosed with stage III metastatic or unresectable disease (79.2 %). Nearly half of the population presented stage IV malignancy at COVID-19 diagnosis. More than 82 % of patients presented comorbidities and up to 51 % had more than three comorbidities, being hypertension (46.3

Table 1
Patient demographics and clinical characteristics.

	N (%)
Sex	
Men	332 (74.3)
Women	115 (25.7)
Smoking status	
Smoker	111 (24.8)
Former smoker (> 1 year)	272 (60.9)
Non-smoker	58 (13.0)
Unknown	6 (1.3)
Type of tumor	
NSCLC	377 (84.5)
SCLC	62 (13.9)
Other	7 (1.6)
Histology	
Adenocarcinoma	228 (51.0)
Adenosquamous	1 (0.2)
Squamous	116 (26.0)
NOS/undifferentiated	20 (4.5)
Unknown	73 (16.3)
Other	9 (2.0)
End-of-life stage	50 (11.2)
Disease status	
Stage III metastatic or unresectable	354 (79.2)
Localized, resectable	28 (6.3)
No evidence of the disease (on follow-up)	60 (13.4)
Unknown	5 (1.1)
Stage at diagnosis of COVID-19	
I	45 (10.1)
II	40 (9.0)
III	144 (32.2)
IV	216 (48.3)
Unknown	2 (0.5)
Number of comorbidities	
0	78 (17.5)
1	1 (0.2)
2	62 (13.9)
3	78 (17.5)
>3	228 (51.0)
Comorbidities[a]	369 (82.6)
Hypertension	207 (46.3)
COPD	137 (30.6)
Cardiovascular disease	114 (25.5)
Diabetes mellitus	102 (22.8)
Other chronic diseases	45 (10.1)

[a] Only the most frequent comorbidities are shown.
COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Table 2
Anticancer and additional treatments.

	N (%)
Anticancer treatment	266 (59.1)
Chemotherapy	
Yes	183 (40.9)
No	83 (18.6)
Unknown	181 (40.5)
Radiotherapy	
Yes	41 (9.2)
No	406 (90.8)
Immunotherapy	
Yes	91 (20.4)
No	356 (79.6)
Treatment line	
Early stage	71 (15.9)
1L	172 (38.5)
2L	64 (14.3)
3L	25 (5.6)
4L	6 (1.3)
Other	9 (2)
Unknown	100 (22.4)
Concomitant medication	
Polypharmacy (≥4)	309 (69.1)
NSAID	81 (18.1)
Corticosteroids	78 (17.5)
ACE inhibitors	74 (16.6)
ARA-II	47 (10.5)
Immunosuppressors	1 (0.2)
Additional treatments	
Antibiotics (n = 430)	328 (73.4)
Hydroxychloroquine (n = 423)	294 (65.8)
Oxygen (n = 426)	269 (60.2)
Anticoagulant (n = 428)	217 (48.5)
Corticosteroids (n = 426)	180 (40.3)
Antivirals (n = 425)	170 (38)
Antibodies (n = 415)	33 (7.4)
Ventilation (n = 396)	14 (3.1)
Antifungals (n = 426)	13 (2.9)
G-CSF (n = 420)	12 (2.7)
Vasoconstrictive (n = 418)	9 (2)
Other (n = 403)	133 (29.8)

ACE, angiotensin converting enzyme; ARA-II, angiotensin II receptor antagonist; G-CSF, Granulocyte colony-stimulating factor; L, line; NSAID, nonsteroidal anti-inflammatory drugs.

%), chronic obstructive pulmonary disease (COPD) (30.6 %), cardiovascular disease (25.5 %), and diabetes mellitus (22.8 %) the most common.

Up to 59.5 % (n = 266) of the population was receiving treatment with anticancer systemic therapy, mainly chemotherapy (40.9 %) and immunotherapy (20.4 %), as early stage (15.9 %) or first-line (1 L) treatment (38.5 %) (Table 2). Patients were also receiving chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (18.1 %), corticosteroids (17.5 %), angiotensin converting enzyme (ACE) inhibitors (16.6 %), and/or angiotensin II receptor antagonists (ARA-II) (10.5 %); nearly 70 % of patients were treated with ≥ four types of medication. Antibiotics (73.4 %), hydroxychloroquine (65.8 %), oxygen (60.2 %), and anticoagulants (48.5 %) were additional treatments commonly administered before hospitalization. Clinical laboratory parameters are shown in Supplementary Table 2.

3.2. Hospitalization

Three-hundred and fifty (78.3 %) patients were hospitalized, with a mean (SD) length of stay of 13.4 (11.4) days (range: 0–90 days). The univariate analysis revealed a significant association between hospitalization and certain variables including clinical laboratory parameters, infection by human immunodeficiency virus (HIV), and the administration of some treatments (Table 3, Supplementary Table 3). The multivariate analysis revealed no further statistical correlation with any of them (Table 4). Similarly, although the duration of hospitalization was initially associated with some clinical laboratory parameters (AST and ALT levels), the concomitant administration of ACE inhibitors, and infection by HIV (Supplementary Table 4), none of these variables statistically correlated with the duration of hospitalization in a multivariate analysis (data not shown). Moreover, our results show that disease status was not a predictor of hospitalization or a hospital longer stay in this population. While the likelihood of hospitalization was higher among patients with stage III metastatic/unresectable disease (79.7 %) compared to those with either no evidence of the disease or localized/resectable disease (20.2 %), similar rates were observed in non-hospitalized patients (80.4 % vs 19.6 %; $p = 0.992$). Overall, 67 patients with localized disease and 264 patients with metastatic disease were hospitalized for 13.5 (11.0) days and 13.3 (11.3) days, respectively ($p = 0.886$).

3.3. ICU admission

Nine of the 447 (2.0 %) patients were admitted to the ICU for a mean (SD) duration of 11.5 (16.3) days (range: 1–50 days). ICU admission was associated with independent variables including the type of cancer ($p = 0.036$), administration of anticancer treatments ($p = 0.049$), clinical laboratory parameters (haemoglobin, $p = 0.030$; prothrombin, $p =$

Table 3
Characteristics of patients according to hospitalization.

	Non-hospitalized patients (n = 97)	Hospitalized patients (n = 350)	*P* value
Age, mean ± SD	65.5 ± 9.4	67.5 ± 9.8	0.075
Smoking history, n (%) (n = 383)	78 (20.4)	305 (79.6)	0.169
Comorbidities, n (%) (n = 369)	77 (20.9)	292 (79.1)	0.435
Type of comorbidities, n (%)*			
Diabetes mellitus (n = 102)	25 (25.8)	77 (22.0)	0.518
Hepatitis (n = 16)	3 (3.1)	13 (3.7)	1
Hypertension (n = 207)	38 (39.2)	169 (48.3)	0.14
COPD (n = 137)	22 (22.7)	115 (32.9)	0.072
Cardiovascular disease (n = 114)	22 (22.7)	92 (26.7)	0.556
Cerebrovascular disease (n = 17)	2 (2.1)	15 (4.3)	0.476
Renal disease (n = 41)	8 (8.3)	33 (9.4)	0.875
End-of-life stage, n (%) (n = 50)	7 (14.0)	43 (86.0)	0.225
Stage at COVID-19 diagnosis, n (%)			
Stage I (n = 45)	8 (17.8)	37 (82.2)	0.641
Stage II (n = 40)	10 (25.0)	30 (75.0)	
Stage III (n = 144)	36 (25.0)	108 (75.0)	
Stage IV (n = 216)	42 (19.4)	174 (80.6)	
Anticancer treatment, n (%) (n = 266)	63 (23.7)	203 (76.3)	0.218
Concomitant medication, n (%)[a]			
NSAID (n = 81)	19 (19.6)	62 (17.7)	0.783
ACE inhibitors (n = 74)	18 (18.6)	56 (16.0)	0.656
ARA-II (n = 47)	8 (8.3)	39 (11.1)	0.525
Corticosteroids (n = 78)	16 (16.5)	62 (17.7)	0.897
Immunosuppressors (n = 1)	0	1 (0.3)	0.711
Polypharmacy (n = 309)	66 (68.0)	243 (69.4)	0.891
Treatments, n (%)[a]			
Antibiotics (n = 328)	32 (37.2)	296 (86.1)	<0.001
Antivirals (n = 170)	5 (5.8)	165 (48.7)	<0.001
Corticosteroids (n = 180)	6 (7.0)	174 (51.2)	<0.001
Hydroxychloroquine (n = 294)	30 (35.3)	264 (78.1)	<0.001
Oxygen (n = 269)	9 (10.6)	260 (76.3)	<0.001
Ventilation (n = 14)	1 (1.2)	13 (4.1)	0.347
Anticoagulant (n = 217)	7 (8.1)	210 (61.4)	<0.001
Laboratory parameters,[b] mean ± SD			
Platelets (n = 60; 337)	252.7 ± 134.7	227.2 ± 13.6	0.175
Neutrophils (n = 60; 336)	5.6 ± 7.3	6.7 ± 6.8	0.249
Lymphocytes (n = 60; 334)	1.4 ± 1.1	0.9 ± 0.8	<0.001
Monocytes (n = 57; 321)	0.5 ± 0.4	0.5 ± 0.3	0.383
NLR (n = 60; 334)	5.9 ± 11.8	10.3 ± 13.4	0.016
CRP (n = 47; 325)	40.6 ± 56.6	57.9 ± 74.6	0.129
Albumin (n = 31; 185)	3.8 ± 0.6	3.5 ± 0.6	0.004
Sodium (n = 58; 333)	137.7 ± 4.2	136.4 ± 4.3	0.037
Fibrinogen (n = 29; 224)	494.4 ± 266.9	616.8 ± 223.6	0.007
LDH (n = 46; 284)	351.4 ± 335.2	403.2 ± 261.4	0.233
DDimer (n = 28; 189)	1151.6 ± 2332.7	2547.8 ± 7093.4	0.303
Prothrombin (n = 38; 271)	36.8 ± 40.8	31.8 ± 34.4	0.423

[a] Percentages were calculated considering the total number of patients hospitalized or non-hospitalized. [b] Laboratory parameters were assessed in (n = non-hospitalized patients; hospitalized patients).
ACE, angiotensin converting enzyme; ARA-II, angiotensin II receptor antagonist; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; LDH, lactate dehydrogenase; NLR, neutrophils/lymphocyte ratio; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

Table 4
Multivariate analysis of factors associated with hospitalization.

	B	E.T.	Wald	gl	Sig.	Exp(B)
Lymphocytes	−0.330	0.310	1.136	1	0.286	0.719
NLR	0.089	0.071	1.577	1	0.209	1.093
Albumin	−0.059	0.497	0.014	1	0.906	0.943
Sodium	0.008	0.014	0.294	1	0.588	1.008
Fibrinogen	0.002	0.001	3.463	1	0.063	1.002
HIV	0.000	0.000	0.124	1	0.725	1.000

HIV, human immunodeficiency virus; NLR, neutrophil/lymphocyte ratio.

0.040), HIV ($p = 0.020$), and treatment with corticosteroids ($p = 0.024$), antibodies, ventilation, and vasoconstrictive agents ($p < 0.001$). The administration of corticosteroids during hospitalization did not increase the rates of ICU admission or mechanical ventilation in this population. None of patients admitted to the ICU received corticosteroids, either as concomitant medication or during hospitalization, while corticosteroids were administered to 4/14 (28.6 %) patients receiving mechanical ventilation.

3.4. Mortality

Of the 447 patients, 146 (32.7 %) died during the study period. Several independent variables significantly correlated with an increased risk of death, including hospitalization, end-of-life stage, stage at COVID-19 diagnosis, the administration of concomitant NSAIDs and other treatments, as well as some clinical laboratory parameters (Table 5 and Supplementary Table 5). The multivariate analysis revealed an increased risk of death in hospitalized, end-of-life stage patients, as well as in those with lymphocytopenia, low albumin, high lactate dehydrogenase (LDH) values, and concomitant administration of NSAIDs (Table 6). Importantly, the administration of anticancer therapies was not associated with an increased risk of death.

Moreover, disease status and the administration of corticosteroids during hospitalization were identified as predictors of mortality in this population. A higher mortality rate was observed in patients with stage III metastatic/unresectable tumours than in those with localized, resectable cancer or no evidence of the disease (86.8 % vs 13.2 %; $p < 0.017$). Likewise, a significantly higher risk of death was found among patients who received corticosteroids during hospitalization compared to those who did not (51.3 % vs 25.7 %; $p < 0.001$). While this association was observed regardless of the chronic administration of corticosteroids, a higher level of significance was found for patients who did not receive this concomitant medication (54.8 % vs 29.1 %; $p < 0.001$) than those who were receiving them (47.2 % vs 30.7 %; $p = 0.024$).

An independent analysis was performed including only hospitalized, non-end-of-life stage patients (n = 307), of whom 107 (34.9 %) died. A statistical correlation was observed between mortality rate and the type of cancer, as well as some clinical laboratory parameters including neutrophils, lymphocytes and LDH (Supplementary Table 6). In the multivariate analysis, a significantly increased risk of death was observed in patients with lymphocytopenia and high LDH values, while no further association was found regarding the administration of concomitant NSAIDs, the type of cancer, or neutrophil values (Supplementary table 7).

3.5. Severity

Overall, 281 (62.9 %) patients presented severe COVID-19, of whom 14 (5.0 %) received mechanical ventilation, 9 (3.2 %) were admitted to the ICU and 126 (44.8 %) died. Significantly higher mortality (44.8 % vs 12.1 %; $p < 0.001$), ICU admission (3.2 % vs 0%; $p = 0.047$), and mechanical ventilation (5.6 % vs 0%; $p = 0.009$) rates were found in severe compared to non-severe COVID-19 patients.

Table 5
Characteristics of patients according to mortality.

	Patients who survived (n = 301)	Patients who died (n = 146)	*P* value
Age, mean ± SD	66.6 ± 9.9	68.0 ± 9.4	0.18
Smoking history, n (%) (n = 383)	255 (66.6)	128 (33.4)	0.463
Hospitalization, n (%) (n = 350)	210 (60.0)	140 (40.0)	<0.001
Comorbidities, n (%) (n = 369)	247 (66.9)	122 (33.1)	0.795
Type of comorbidities, n (%)[a]			
Diabetes mellitus (n = 102)	75 (24.9)	27 (18.5)	0.162
Hepatitis (n = 16)	12 (4.0)	4 (2.7)	0.694
Hypertension (n = 207)	134 (44.5)	73 (50.0)	0.323
COPD (n = 137)	95 (31.6)	42 (28.8)	0.623
Cardiovascular disease (n = 114)	69 (22.9)	45 (30.8)	0.093
Cerebrovascular disease (n = 17)	9 (3.0)	8 (5.5)	0.304
Renal disease (n = 41)	30 (10.0)	11 (7.5)	0.509
End-of-ilfe stage, N (%) (n = 50)	16 (32.0)	34 (68.0)	<0.001
Stage at COVID-19 diagnosis, n (%)			
Stage I (n = 45)	33 (73.3)	12 (26.7)	0.005
Stage II (n = 40)	30 (75.0)	10 (25.0)	
Stage III (n = 144)	109 (75.7)	35 (24.3)	
Stage IV (n = 216)	128 (59.3)	88 (40.7)	
Anticancer treatment, n (%) (n = 266)	183 (68.8)	83 (31.2)	0.462
Concomitant medication, n (%)[a]			
NSAID (n = 81)	46 (15.3)	35 (24.0)	0.035
ACE inhibitors (n = 74)	55 (18.3)	19 (13.0)	0.205
ARA-II (n = 47)	30 (10.0)	17 (11.6)	0.106
Corticosteroids (n = 78)	45 (15.0)	33 (22.6)	0.062
Immunosuppressors (n = 1)	0	1 (0.7)	0.711
Polypharmacy (n = 309)	207 (68.8)	102 (69.9)	0.9
Treatments, n (%)[a]			
Antibiotics (n = 328)	203 (71.0)	125 (86.8)	<0.001
Antivirals (n = 170)	102 (36.0)	68 (47.9)	0.025
Corticosteroids (n = 180)	87 (30.7)	93 (65.0)	<0.001
Hydroxychloroquine (n = 294)	204 (71.8)	90 (64.8)	0.17
Oxygen (n = 269)	145 (51.1)	124 (87.3)	<0.001
Ventilation (n = 14)	7 (5.4)	7 (2.6)	0.26
Anticoagulant (n = 217)	126 (44.2)	91 (63.6)	<0.001
Laboratory parameters,[b] mean ± SD			
Platelets, (n = 258; 139)	248.7 ± 142.9	198.2 ± 108.5	<0.001
Neutrophils (n = 258; 139)	5.8 ± 6.4	7.7 ± 7.6	0.009
Lymphocytes (n = 256; 138)	1.1 ± 0.9	0.7 ± 0.7	<0.001
Monocytes (n = 245; 133)	0.5 ± 0.3	0.5 ± 0.3	0.034
NLR (n = 256; 138)	6.8 ± 8.3	14.9 ± 18.3	<0.001
CRP (n = 239; 133)	45.4 ± 64.4	74.2 ± 82.8	<0.001
Albumin (n = 142; 74)	3.7 ± 0.6	3.2 ± 0.6	<0.001
Triglycerides (n = 53; 26)	131.6 ± 65.1	165.7 ± 71.3	0.037
Glycemia (n = 211; 112)	121.0 ± 46	138.0 ± 65	0.009
LDH (n = 217; 113)	348.7 ± 230.9	486.7 ± 321.5	<0.001
DDimer (n = 147; 70)	2119.5 ± 6029.8	2888.6 ± 7910.3	0.429
Prothrombin (n = 200; 109)	31.8 ± 35.8	33.6 ± 34.4	0.676

[a] Percentages were calculated considering the total number of patients who survived or died. [b] Laboratory parameters were assessed in (n = patients who survived; patients who died).
ACE, angiotensin converting enzyme; ARA-II, angiotensin II receptor antagonist.; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; LDH, lactate dehydrogenase; NLR, neutrophils/lymphocyte ratio; NSAID, nonsteroidal anti-inflammatory drugs.

4. Discussion

The GRAVID study reports one of the largest series of patients with lung cancer and COVID-19 diagnosis to date. Most patients were older than 60 years, had advanced stage or metastatic NSCLC and presented numerous comorbidities, including those associated with an increased risk of SARS-CoV-2 infection and severe outcomes. Our results reveal high hospitalization and mortality rates but low ICU admission in patients with lung cancer, despite a majority of patients developed severe COVID-19, in line with previous studies. [4,6] Notably, the administration of corticosteroids during hospitalization and stage III metastatic or unresectable disease were identified as predictors of mortality, emphasizing the need for close monitoring in this subpopulation.

Table 6
Multivariate analysis of factors associated with mortality.

	B	E.T.	Wald	gl	Sig.	Exp(B)
Hospitalization	−1.509	0.612	6.074	1	0.014	0.221
End-of-life stage	−1.771	0.613	8.355	1	0.004	0.170
NSAIDs	−1.453	0.522	7.743	1	0.005	0.234
Lymphocytes value	1.177	0.369	10.153	1	0.001	3.245
Albumin value	0.651	0.199	10.740	1	0.001	1.918
LDH value	−0.002	0.001	9.642	1	0.002	0.998

NSAID, nonsteroidal anti-inflammatory drugs; LDH, lactate dehydrogenase.

COVID-19 mortality rates in patients with cancer, while high, seem to vary across studies, probably due to the inclusion of patients with different types of tumours and disease status, as well as differences in the use and availability of intensive care resources. [10] According to a recent meta-analysis, a 25.6 % probability of death (95 % CI: 22.0 %–29.5 %) was estimated among 18 650 cancer patients [20]. Our data suggest that mortality might be higher in lung cancer patients (32.7 %), as expected due to their pre-existing lung damage and associated comorbidities. Similar results were reported from the TERAVOLT registry in patients with thoracic malignancies [4], and a cohort study performed by the UK Coronavirus Cancer Monitoring Project (UKCCMP) [6]. In contrast, the Gustave Roussy cohort showed a lower mortality rate among patients mostly with ECOG performance status 0–1 and a history of solid tumours [3]. More recently, the French nationwide cohort study (GCO-002 CACOVID-19) reported 29 % deaths among 1289 patients with cancer and COVID-19 [10]. In line with the TERAVOLT, UKCCMP, and CACOVID-19 studies [4,6,10], the rate of ICU admission during the pandemic was relatively low among patients of the GRAVID population, which could be explained by general ICU policies applied in areas of high COVID-19 incidence.

In light of the evidence suggesting that cancer patients with COVID-19 present worse clinical outcomes than non-cancer patients, numerous studies have been performed to elucidate the risk factors associated with poor prognosis. [3–5,7,10,19,21] A cohort study of 1035 records from the COVID-19 and Cancer Consortium database reported that advanced age, male sex, smoking status, number of comorbidities, ECOG ≥ 2, active cancer, and receipt of azithromycin plus hydroxychloroquine were associated with increased 30-day mortality [5]. In contrast to previous reports [4,10], smoking history was not associated with an increased risk of death among the GRAVID population, which might be due to the small proportion of current smokers. Noticeably, we confirmed that a reduced probability of survival was associated with lymphocytopenia and with low albumin and high LDH levels, in line with previous evidence. [3,12]

Since severe forms of COVID-19 may be treated with corticosteroids, caution should be given to patients who may already be receiving this medication as part of their cancer care. Results from studies of corticosteroids in the treatment of COVID-19 in non-cancer patients are mixed in terms of survival benefit, [22] while only a few studies have been performed in patients with cancer. Combined data from the Hubei, CACOVID-19, and TERAVOLT cohorts suggest that corticosteroid use, either as part of cancer care or to treat COVID-19, may increase the risk of death. [10,23,24] Accordingly, our results revealed a significantly higher mortality rate in patients who received corticosteroids during hospitalization, which doubled the risk of death observed in their non-treated counterparts. Taking into account previous data showing a

tendency between the risk of death and the use of corticosteroids before COVID-19 diagnosis [10], our findings suggest that the administration of corticosteroids as anticancer and anti−COVID-19 treatment might have a synergic deleterious effect. Of note, corticosteroids might have been administered as conservative treatment in patients who were deemed not to be candidates for ICU admission.

Given the plausible link of NSAIDs with an exacerbation of respiratory and cardiovascular complications in various infection settings, a pragmatic and cautionary approach of avoiding NSAIDs as first-line treatment for managing COVID-19 symptoms is generally recommended. [25] In the GRAVID population, NSAIDs were administered as concomitant medication to anticancer treatment in higher proportion of patients than reported in previous studies [4,10]. Although the administration of NSAIDs was initially identified as a risk factor for mortality in the analysis of the overall GRAVID population, no further association was observed among hospitalized, non-end-of-life patients. Similarly, data from the CACOVID-19 cohort failed to show an increased risk of death due to NSAIDs consumption [10]. Considering that patients with cancer may be receiving NSAIDs at COVID-19 diagnosis, particularly in advanced and end-of-life stages, its potential deleterious effect should not be neglected, and caution should be exercised until further evidence emerges.

Despite the worrying initial data, [24] the administration of anticancer systemic therapies has not been shown to impact on the survival of patients with cancer and COVID-19. Large COVID-19 cancer cohorts that mostly included patients with solid organ tumours have revealed no significant increased mortality risk or clinical worsening related to recent chemotherapy, immunotherapy, or radiotherapy [3–5,10,21]. Moreover, while patients with lung cancer may present higher rates of severe or critical illness, the incidence of these events seemed similar regardless the administration of cytotoxic chemotherapy or immunotherapy [12]. Our findings further support these results, showing no correlation between the administration of anticancer therapies and the likelihood of hospitalization, ICU admission, or survival in lung cancer patients. Therefore, the risk of mortality stemming from withdrawing or discontinuing these therapies should be balanced by the potential risk of a life-threatening COVID-19 infection.

Oncological care has been impacted by the pandemic, due to shortages in health service capacity and resources. According to a survey conducted in the Netherlands, up to 30 % of patients with cancer have reported consequences in their cancer care follow-up. [26] Moreover, interruption or suspension of systemic anticancer treatments was reported in 39 % patients of the CACOVID-19 cohort following COVID-19 diagnosis [10]. To prioritize the prevention, detection, and treatment of patients with thoracic cancers, expert-based recommendations have been published by collaborative groups worldwide [13–17,27,28], aimed at standardizing management and providing guidance to the oncology community [29]. It is generally recommended that the principles of lung cancer treatment should be followed, especially in cases in which a delay may result in rapid cancer progression [29]. Individualized approaches are strongly advised to ensure effective cancer treatment while minimizing the risk of exposure to SARS-CoV-2, considering the risk/benefit ratio for each patient.(2728)

Our study had some limitations. Results may be partially biased by the inclusion of patients with adverse COVID-19 outcomes since cancer patients with less severe infections may not have needed medical attention during the study period. During hospitalization, neither the dose nor type of administered corticosteroids were registered. Additionally, we did not compare all-cause mortality, characteristics, outcomes, and treatment strategies of patients with cancer against a control group of non-cancer patients. Nonetheless, the sample size was large enough to provide a broad overview on the impact of COVID-19 on patients with lung cancer in Spain, and to show which characteristics are strongly associated with poor prognosis.

5. Conclusions

The GRAVID study provides one of the largest overviews on the impact of COVID-19 in patients with lung cancer to date. In addition to their potential immunocompromised status and cancer-related features, this nationwide cohort presented most of the COVID-19-associated risk factors for severity and poor prognosis, such as older age, comorbidities, and smoking history. Mortality was high and associated with the general characteristics of cancer patients, advanced disease, and the administration of corticosteroids during hospitalization. Although systemic anticancer therapies did not increase the risk of death, management of these patients should carefully consider a balance between the risks and benefits of safely delivering anti−COVID-19 treatments alongside anticancer therapy. Our findings may inform physicians on patient's prognosis and assist in guiding healthcare decisions.

Author contributions

Dr Provencio had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Funding

This study was funded by the Spanish Lung Cancer Group and Novartis. The funders of the study had no role in data collection, data analysis, data interpretation, or writing of the report.

Ethics statement

This study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Protocol approval was obtained from the institutional review board of the Hospital Universitario Puerta de Hierro-Majadahonda (Madrid, Spain) (PI 51/20).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors received medical writing support in the preparation of this manuscript from Celia Miguel Blanco (Medical Statistics Consulting, S.L., Valencia, Spain). The authors thank Dr Cristina Avendaño (Hospital Universitario Puerta de Hierro-Majadahonda) for her advice and support in the Ethic Committee submission. We also thank all investigators who participated in the GRAVID study: Dr Manuel Cobo (Hospital Regional de Málaga), Dr Guillermo López Vivanco (Hospital Universitario De

Cruces), Dr María Guirado (Hospital General de Elche), Dr Víctor Amezcua Hernández (Hospital Universitario Virgen de las Nieves), Dr Pilar López Criado (MD Anderson), Dr María del Rosario Hernández (Hospital Nuestra Señora Sonsoles), Dr Beatriz Losada (Hospital Universitario de Fuenlabrada), Dr Sergio Vázquez Estevez (Hospital Universitario Lucus Augusti), Dr Silvia Muñoz (Hospital General de Granollers), Dr Laia Capdevila Riera (Hospital Sant Pau i Sant Tecla Tarragona), Dr Delvys Rodríguez (Hospital Universitario Insular), Dr Jorge José García (Hospital Clínico Universitario de Santiago), Dr Sergio Peralta Muñoz (Hospital Sant Joan de Reus), Dr José David Cumplido (Hospital de Torrevieja), Dr Sara Cerezo (Hospital la Mancha Centro), Dr Judit Rubio Martínez (Hospital Universitario de Móstoles), Dr Raquel Cervera (Hospital Universitario del Henares), Dr Bartomeu Massutí (Hospital General de Alicante), Dr Oscar Juan Vidal (Hospital Politècnic i Universitari La Fe), Dr Amelia Insa (Hospital Clínico Valencia), Dr Pilar Lianés (Hospital de Mataró), Dr Airam Padilla (Hospital Universitario Nuestra Señora de Candelaria), Dr Ignacio Gil Bazo (Clínica Universidad De Navarra), Dr Idoia Morilla (Complejo Hospitalario de Navarra), Dr Jesús Corral (Clínica Universidad de Navarra), Dr Karmele Areses (Hospital Santa María Nai), Dr José García Sánchez (Hospital Arnau de Vilanova), Dr Juan Coves Sarto (Hospital Universitario Son Llàtzer), Dr Inmaculada Maestu (Hospital Universitario Dr. Peset), Dr Marta Zafra (Hospital Morales Meseguer), Dr Elisa Gálvez (Hospital General de Elda), Dr Jenifer Gómez Mediavilla (Instituto Onkologikoa), Dr Rosa María Villatoro (Hospital Costa del Sol), Dr Mónica Serrano Gómez (Hospital de Manises), Dr Ángela Moreno Martí (Hospital Verge de la Cinta), Dr Amaia Moreno (Hospital Universitario de Galdakao Usansolo), Dr Mª Ángeles Moreno Santos (Hospital Puerto Real), and Dr José Luis Monroy Antón (Hospital Universitario de la Ribera); and thanks to Eva Pereira, Julita Ocaña and Lorena Garcia for coordinating the study in the Spanish Lung Cancer Group.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.05.014.

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