Peer review file

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Reviewer A

C1: "*This study area and methods are overlapped previous studies such as Kwang-Ho in (2005). I think the authors needs to improve the focus on the benefit of Fast Diagnostic Track."*

R1: We appreciate the Reviewer's comment. We have become aware of the importance of performing our work specifically from an optimal care pathway, the lung cancer fast diagnostic track (FDT). We have highlighted its value in the introduction section (Page 4, Lines 19-25), expanded its description in material and methods section (Page 5, Line 15-18; Page 6, Lines 3-19), and explained its relevance in the discussion section (Page 13, Lines 19-24; Page 14, Lines 1-4). After having compared the methodology of previous similar bibliography on symptomatology and prognosis in patients with lung cancer, such as that of Kwan-Ho *et al* [1], Kocher *et al* [2] or Sheel *et al* [3], there are noteworthy differences with our work. The data collection in these cases has been based on databases from surveys [1] and hospital records [2,3], but the underlying clinical practice has not been specified to be performed from a fast diagnostic pathway. The fact that our results come from this model of care, which aims to maintain a high quality of care for patients with suspected lung cancer, especially with regards to timely care, adds additional weight and robustness to the study.

Reviewer B

"*In this manuscript entitled "Prognostic Value of Symptoms at Lung Cancer Diagnosis: A Three-Year Observational Study" by Dr. Dinora Polanco et al., the authors explored the prognostic impact of physical symptoms at diagnosis for lung cancer patients across stage or histology. In my opinion, substantial revisions are needed to consider this manuscript for publication. Please see my comments below. I hope my comments are*

useful for improvement of the article."

Major

C1: "*The authors stated that novelty of this study based on its targeted population (any stage or histology). I agree that early detection of lung cancer is crucial, and this would be a key message from this analysis. However, it is still unclear why this research was needed to be conducted over preceding literatures, in relatively small size scale. Although the prognostic impact of initial symptoms was shown in overall population, the sample size in each stage is small, which might make the readers interpret the data in terms of clinical utility. The authors are strongly encouraged to reconsider the presentation of this study's novelty or strength."*

R1: We thank the Reviewer for his interesting observation that takes into account the usefulness of our work for readers and that makes us reflect on its novelty. This observation is in line with the comment made by Reviewer A, and has led to us analyzing in detail what differentiates our work from previous studies. With respect to previous literature, a differential fact of great transcendence is that our work has been carried out from an optimal care pathway, the lung cancer fast diagnostic track (FDT), something that has not been remarked by its predecessors, which were mainly based on databases from surveys [1] and hospital records [2,3]. Optimal care pathways are structured and multidisciplinary care plans for a specific clinical condition, which describe a task to be pursued, its timing, sequence and professionals involved [4]. Benefits of this model of care have been shown in previous literature, with an overall improvement in patient's satisfaction and timeliness of care, or a reduction in costs [5].We believe that a centralized management of all lung cancer cases from an entire health care area, in an optimal care pathway specifically designed to carry out a timely management of the highest quality and adherent to guidelines, provides a high methodological quality to the work underlying our study, and we believe this is one of its strengths. Taking this into account, as detailed in C1 of Reviewer A, we have highlighted the FDT value in the introduction section (Page 4, Lines 19-25), expanded its description in material and methods section (Page 5, Line 15-18; Page 6, Lines 3-19), and explained its relevance in the discussion section (Page 13, Lines 19-24; Page 14, Lines 1-4)

Minor

C2: *"Page 4, line 10: "any radiologically suspicious~" Please specify the modality of radiological evaluation. Were the abnormal opacities detected by plaint chest X-ray or CT scan?"*

R2: We appreciate the Reviewer's commentary, and based on it we have specified in the methods section the radiological images referred to (Page 5, Line 19-21). The radiological modalities by which patients can be referred to the lung cancer fast diagnostic track (FDT) can be both chest X-ray, and CT scan. In cases where the patient has only had a chest X-ray, from the lung cancer FDT the evaluation is completed with a CT scan. The present study only takes into account the first imaging modality (either chest X-ray or CT scan) in which the suspicious lesion was evidenced for the first time, and which motivated the referral of the patient to the consultation.

C3: "*Page 7, line 2: "toxic syndrome" This term would be ambiguous and unclear. Please paraphrase it in other common medical term."*

R3: We thank the Reviewer's suggestion and in order to avoid confusing terms we have modified the expression "toxic syndrome" to "constitutional syndrome" throughout the new version of the manuscript (Page 8, Line 7; Page 21, Table 2).

C4: *"Table 1: "Histology" Please specify the details of "other" histology in the foot note."*

R4: Attending to the Reviewer's remark, we have specified in detail "other" histologies in the footnote of Table 1 (Page 19, Table 1; Page 20, Line 3-5).

C5: *"Table 1: Palliative -> Best supportive care."*

R5: As suggested by the Reviewer, we have changed the term "palliative" for "best

supportive care" throughout the text (Page 9, Line 1; Page 19, Table 1).

C6: *"Table 2: Please show the breakdown of each symptom by stage (I, II, III, and IV)."*

R6: Following the Reviewer's suggestion, we have modified Table 2, detailing the symptoms of presentation in the different stages (Page 21, Table 2). We provide this table below that has been introduced in the new manuscript as new Table 2, as well as its relevant information in the text (Page 10, Lines 9-12).

Table 2: Leading symptoms in symptomatic patients categorized by stage.

Symptoms	**ALL N=200****	**I N=21**	**II N=7**	**III N=60**	**IV N=112**
Respiratory Symptoms, n (%)					
Cough	40 (20.0)	0 (0.00)	2 (28.6)	19 (31.7)	19 (17.0)
Dyspnea	20 (10.0)	0 (0.00)	0 (0.00)	7 (11.7)	13 (11.6)
Hemoptysis	23 (11.5)	3 (14.3)	2 (28.6)	5 (8.33)	13 (11.6)
Chest pain	20 (10.0)	1 (4.76)	1 (14.3)	8 (13.3)	10 (8.93)
Exacerbation/respiratory infection	30 (15.0)	10 (47.6)	2 (28.6)	10 (16.7)	8 (7.14)
Non-respiratory symptoms, n (%)					
Musculoskeletal pain	23 (11.5)	4 (19.0)	0 (0.00)	2 (3.33)	17 (15.2)
Dysphagia	3 (1.50)	0 (0.00)	0 (0.00)	1 (1.67)	2 (1.79)
Neurological deficits	5 (2.50)	0 (0.00)	0 (0.00)	0 (0.00)	5 (4.46)
Constitutional syndrome	25 (12.5)	3 (14.3)	0 (0.00)	4 (6.67)	18 (16.1)
Other symptoms*	11 (5.50)	0 (0.00)	0 (0.00)	4 (6.67)	7 (6.25)

* Other symptoms: hoarseness, superior vena cava syndrome, abdominal pain and palpation of subcutaneous lesion. **From symptomatic patients (n=201), one has missing information about stage.

C7: *"Table 1: Please specify the details of "other symptoms" in the foot note."*

R7: Attending to the Reviewer's remark, we have specified in detail "other" symptoms in the footnote of Table 2 (Page 21, Table 2, Line 4).

C8: *"Figure 2: What if the symptomatic patients were divided into "Respiratory" and "Non-respiratory"? Additional exploration on this point may help deepen the discussion and find some novelty from this research."*

R8: Following on from the Reviewer's suggestion we have deepened into the exploration of the prognostic value of the type of symptomatology presented by patients, analyzing differences between groups and survival categorizing them into three categories: asymptomatic patients, patients with respiratory symptoms and patients with non-respiratory symptoms. Here we provide a new table called Table A (supplemental material, Page 2-3, Table A), where asymptomatic patients are compared to both categories of symptomatic patients. As you can see, asymptomatic patients were significantly older than patients presenting with respiratory symptoms, but this was not the case of patients with non-respiratory presentation. However, no significant differences were observed regarding age between symptomatic respiratory and non-respiratory patients. Also, asymptomatics presented significantly more frequently with stage I disease, while symptomatics present more frequently with stages III and IV (non-respiratory patients) and IV (respiratory patients). Finally, with regard to initial treatment, asymptomatics underwent surgery more frequently, while symptomatics were more frequenly put through chemotherapy or chemoradiotherapy. We also provide a new figure called Figure B (supplemental material, Page 4, Figure B), where Kaplan Meier survival curves of these three groups are presented. As you can observe, there is a significant difference between asymptomatic patients and the two categories of symptomatic ones (HR included in Figure B). However, no significant difference was observed between the categories within the symptomatic group (p=0.2). As a last

point, Cox regression analysis was performed to clarify the effect of symptomatic status, differentiating between respiratory and non-respiratory symptoms, and is here provided as Figure C (supplemental material, Page 5, Figure C). After adjusting the model for age, sex, disease stage and ECOG scale, both symptomatic presentations confirmed to be independent prognostic factors of non-survival, with a HR of 2.71 for respiratory symptoms and 2.47 for non-respiratory symptoms.

Given the purpose of this paper, which is to highlight survival differences in lung cancer patients according to their clinical presentation, and taking into account that no survival differences where appreciated between both patients with respiratory and non-respiratory symptoms, our proposal is as follows: to maintain Table 1 (Page 19-20, Table 1) provided on first manuscript and considering only two categories, asymptomatic and symptomatic patients. Additional information of these considerations regarding the nature of symptoms, will be provided as supplementary material (Page 11, Lines 4-9).

Table A. Clinical and demographic characteristics of the patients categorized on asymptomatics, symptomatics with respiratory symptoms and symptomatics with non-respiratory symptoms.

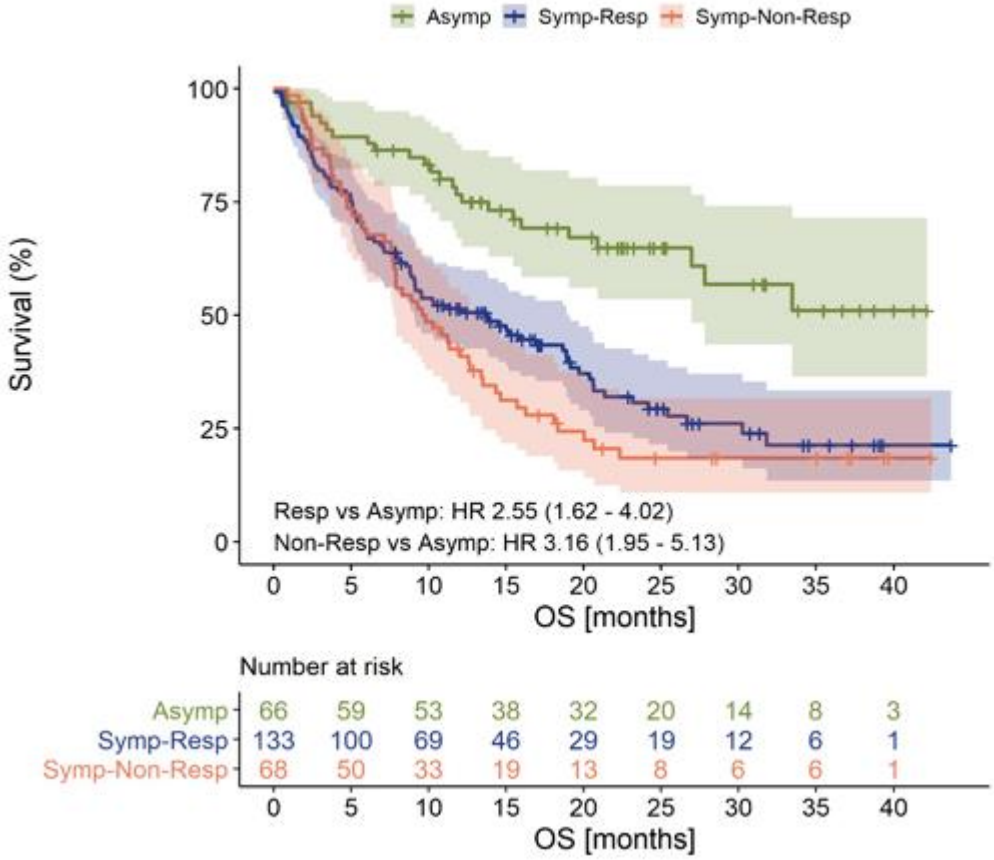
Variables	ALL N=267	Asymptomatic N=66	Symptomatic - Respiratory N=133	Symptomatic - Non-respiratory N=68	p.Asymptomatic vs Symptomatic - Respiratory	p.Asymptomatic vs Symptomatic - Non-respiratory	p.Symptomatic - Non-respiratory vs Symptomatic - Respiratory
Age	68.0 (10.7)	70.9 (9.92)	65.8(10.4)	67.7 (10.9)	0.015	0.105	0.454
Sex, male, n (%)	223 (83.5%)	55 (83.3%)	54(79.4%)	114 (85.7%)	0.817	0.817	0.817
Stage, n (%)					<0.001	<0.001	0.001
I	46 (17.3%)	25 (37.9%)	7(10.4%)	14 (10.5%)			

II	16 (6.02%)	9 (13.6%)	0(0.00%)	7 (5.26%)			
III	78 (29.3%)	18 (27.3%)	11 (16.4%)	49 (36.8%)			
IV	126 (47.4%)	14 (21.2%)	49(73.1%)	63 (47.4%)			
Smoking status, yes, n(%)	133 (86.4%)	29 (85.3%)	39(84.8%)	65 (87.8%)	1.000	1.000	1.000
Total tobacco exposure, median [p_{25th};p_{75th}]	50.0 [30.0;68.5]	50.0 [31.2;60.0]	46.0 [30.0;68.5]	50.0 [35.0;75.0]	0.837	0.337	0.337
FEV_1/FVC, < 70, n (%)	115 (54.0%)	31 (49.2%)	21(50.0%)	63 (58.3%)	1.000	0.689	0.689
FEV_1 %, mean (SD)	74.5 (21.4)	77.4 (22.7)	77.2(19.5)	71.8 (21.3)	0.999	0.237	0.347
DLCO, mean (SD), ml CO/min/mmHg	67.6 (18.0)	67.2 (19.6)	69.3(16.7)	67.1 (17.5)	0.846	0.999	0.802
Histology, n (%)					0.720	0.720	0.720
Squamous	91 (34.1%)	24 (36.4%)	19(27.9%)	48 (36.1%)			
Adenocarcinoma	110 (41.2%)	29 (43.9%)	29(42.6%)	52 (39.1%)			
Small cell lung cancer	37 (13.9%)	8 (12.1%)	13(19.1%)	16 (12.0%)			
Other*	29 (10.9%)	5 (7.58%)	7(10.3%)	17 (12.8%)			
Deaths, n (%):	164 (61.4%)	24 (36.4%)	53(77.9%)	87 (65.4%)	<0.001	<0.001	0.096
Initial treatment, n (%)					<0.001	<0.001	0.961
Surgery	56 (21.2%)	28 (42.4%)	8(11.9%)	20 (15.3%)			

Chemotherapy	117 (44.3%)	20 (30.3%)	35(52.2%)	62 (47.3%)			
Chemoradiotherapy	57 (21.6%)	8 (12.1%)	16(23.9%)	33 (25.2%)			
Radiotherapy	17 (6.44%)	7 (10.6%)	3(4.48%)	7 (5.34%)			
Best supportive care	17 (6.44%)	3 (4.55%)	5(7.46%)	9 (6.87%)			
ECOG scale, n (%)					0.929	0.913	0.913
0-1	220 (86.6%)	52 (85.2%)	54(83.1%)	114 (89.1%)			
>1	34 (13.4%)	9 (14.8%)	11(16.9%)	14 (10.9%)			

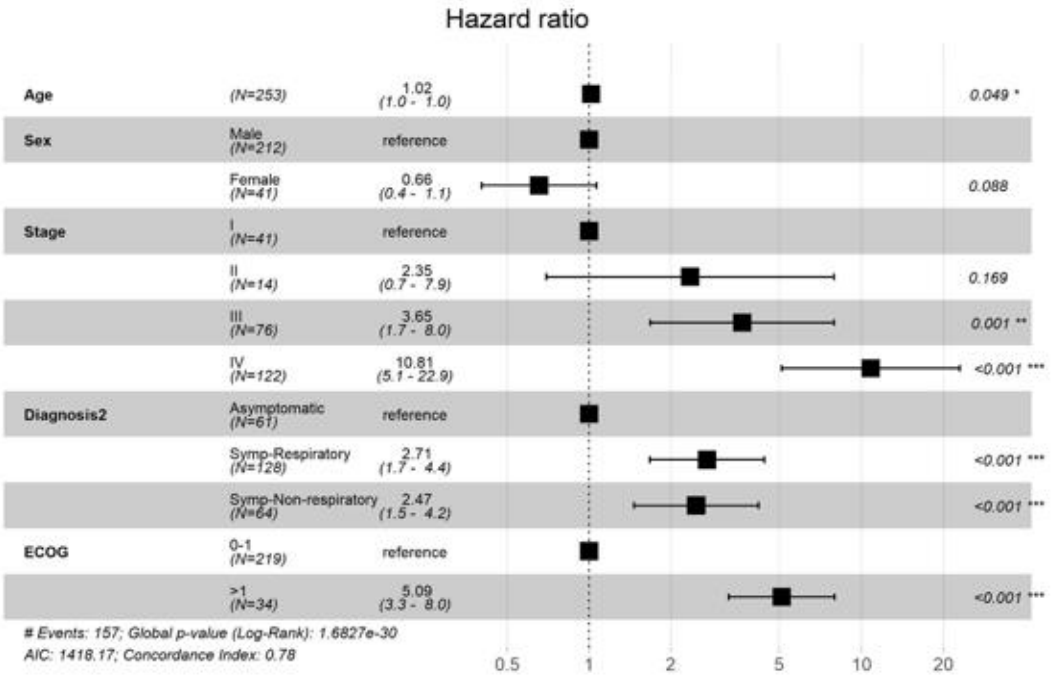
SD: Standard deviation; p25th;p75th: 25 and 75 percentiles; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity. DLCO: the diffusion capacity of carbon monoxide. ECOG: Eastern Cooperative Oncology Group. Total tobacco exposure is expressed in pack-years. *Other histologies: large cell neuroendocrine carcinoma, carcinoid tumors (typical and atypical), adenosquamous carcinoma and undifferentiated non-small cell lung cancer-not otherwise specified (NOS).

Figure B: Kaplan-Meier curve of the time between diagnosis and all-cause death between patients who were asymptomatic, symptomatic with respiratory symptoms and symptomatic with non-respiratory symptoms at diagnosis



Resp: symptomatic patients with respiratory symptoms. Asymp: asymptomatic patients. Non- Resp/ Symp-Non-Resp: symptomatic patients with non-respiratory symptoms. HR: Hazard Ratio. OS: Overall Survival

Figure C: Multivariate Cox regression analysis adjusted by age, sex, disease stage, symptoms at diagnosis and ECOG scale



ECOG: Eastern Cooperative Oncology Group

Reviewer C

This work presents data from everyday clinical practice on a general population of patients with suspicion of lung Cancer. The author's primary conclusion was that asymptomatic patients have a better prognosis than those presenting with cancer-related symptoms. The manuscript is interesting, however, I have the following comments:

C1: "*Were there any differences concerning comorbidity in both groups? Please provide and compare data on e.g. rates of COPD, CHF, etc...*"

R1: The Reviewer has suggested the very interesting topic of comorbidities. Reports on the impact of comorbidities on lung cancer survival have been conflicting [6], but, especially in population-based studies, an association has been found between comorbidity and survival [7, 8]. Therefore, based on your suggestion, we have analyzed and compared the data of the main comorbidities and the overall score obtained using the age-adjusted Charlson Comorbidity Index (ACCI) [9] between asymptomatic and symptomatic patients. The additional results can be found in Table 1 as well as in the text of the new manuscript (Page 7, Line 24; Page 8, Lines 1-2; Page 10, Lines 6-7; Page 12, Lines 11-14). As you can see, no significant differences were observed on the ACCI score between both groups. In the individual analysis of comorbidities, only statistically significant differences were observed in chronic obstructive pulmonary disease (COPD) and cerebrovascular disease, so that asymptomatic patients had a higher prevalence of these conditions. The explanation we attribute to this finding is that patients with the above comorbidities, especially patients with COPD, can undergo more through routine radiological studies, in which the incidental finding of a clinically asymptomatic malignant lesion may occur.

Additional information to **Table 1:** Clinical and demographic characteristics of the patients.

Variable	ALL N=267	Asymptomatic N=66	Symptomatic N=201	p.overall	N

ACCI score, median [p_{25th};p_{75th}]	7.00 [5.00;9.00]	7.00 [5.00;8.75]	7.00 [5.00;9.00]	0.087	267
Myocardial infarction, n(%)	28 (10.5%)	10 (15.2%)	18 (8.96%)	0.232	267
Congestive heart failure, n(%)	10 (3.75%)	2 (3.03%)	8 (3.98%)	1.000	267
Peripheral vascular disease, n(%)	30 (11.2%)	8 (12.1%)	22 (10.9%)	0.970	267
Cerebral vascular disease, n(%)	18 (6.74%)	9 (13.6%)	9 (4.48%)	0.020	267
Dementia, n(%)	7 (2.62%)	2 (3.03%)	5 (2.49%)	0.684	267
Chronic obstructive pulmonary disease, n(%)	122 (45.7%)	39 (59.1%)	83 (41.3%)	0.018	267
Diabetes, n(%)	78 (29.2%)	23 (34.8%)	55 (27.4%)	0.315	267
Diabetes with end-organ damage, n(%)	11 (4.12%)	3 (4.55%)	8 (3.98%)	0.736	267
Moderate/severe renal disease, n(%)	16 (5.99%)	3 (4.55%)	13 (6.47%)	0.768	267
Moderate/severe liver disease, n(%)	11 (4.12%)	2 (3.03%)	9 (4.48%)	1.000	267

C2: "*Patients in the asymptomatic Group were older and presented more often with early stage lung cancer. It is well known, that aggressive cancer is seldom asymptomatic. Therefore, it would be interesting to see whether cancer in symptomatic patients presented with e. g. higher Ki67 or elevated LDH.*"

R2: The Reviewer makes an interesting observation with regards to tumor aggressiveness biomarkers. Patients who are referred to our lung cancer fast diagnostic track (FDT) come with a basic blood test, usually requested by his own family doctor, which includes a biochemistry, a blood count and a clotting test. Sometimes, this includes the lactate dehydrogenase (LDH) parameter. However, the number of patients with this parameter was very small (n=24), which is why we decided not to include it in the analysis.

With respect to Ki-67, in our centre this determination is routinely made only in neuroendocrine tumors of carcinoid type, and not in other histological types. It is for this reason that this data is not currently available in the database.

Based on your accurate comment, and since we cannot provide data on tumor

aggressiveness, we have dinclude this component as a limitation in the limitation section of the manuscript (Page 13, Line 16-18).

C3: "*Table 2: please provide more Information on toxic syndroms and add a list for other Symptoms."*

R3: As the Reviewer rightly suggests, and has also been suggested by Reviewer B, the term "toxic syndrome" is ambiguous and confusing, and has been replaced by the term "constitutional syndrome" which is the symptom it refers to (Page 8, Line 7; Page 21, Table 2). Besides, we have specified in detail "other" symptoms in the footnote in Table 2 (Page 21, Table 2, Line 4).

C4: "*Figure 3: The presented data give information on univariable Cox Regression analysis. Showing this you confirm well-known prognostic factors like sex, disease stage and PS. Multivariable analysis is needed to see wheter the item "symptomatic/asymptomatic" really is an Independent prognostic factor. Furthermore, age-adjusted data are missing. You also should integrate (if available) Information on the respective cancer aggressiveness in your model as mentioned above. From my point of view, the initial treatment modality is just a surrogate for disease stage (and probably PS) and thus not represents an Independent prognostic variable. It would be interesting to see (beside the multivariable Cox Regression) Kaplan-Meier curves adjusted for age, sex, ECOG-PS and disease stage. In conclusion, I suggest to perform a 1:1 propensity score matched pairs analysis for the mentioned prognostic factors.*``

R4: As the reviewer correctly remarks, a multivariable analysis is needed to see if the symptomatic/asymptomatic item has prognostic value. The provided figure 3 is a multivariate analysis which serves this purpose, however it was not well reflected in the figure's title, therefore we have proceeded to correct it so that no doubts can arise from the readers (Page 24, Figure 3). We have reflected on the observation made by the reviewer on including initial treatment in the multivariate model, which had initially been included based on previous literature (2). However, based on your suggestion and

given the nature probably surrogate of this item, we present a Cox regression model not adjusted by treatment. We now provide you with an updated Multivariate Cox regression analysis in Figure 3 of the new manuscript, correcting population included in the model (missings in confounders), and adjusting the model as previously by age, sex, stage and ECOG-PS.

With respect to the second question, and in relation to the previously answered C2 comment, no data is available regarding biological parameters of aggressiveness to be added to the Cox regression model. Again, we will add this point in the limitation section (Page 13, Line 16-18).

Finally, we appreciate the interesting suggestion made by the Reviewer regarding the performance of a 1:1 propensity score matched pairs analysis. After performing this, we have corroborated that after adjusting for age, sex, stage and ECOG-PS, differences in survival curves remain statistically significant between symptomatic and asymptomatic patients (p=0.041) (Page 9, Lines 15-18; Page 10, Lines 22-24; Page 11, Lines 1-3). We are providing this additional figure encoded as Figure E, along with the table including paired matched patients as supplemental Table D (supplemental material, Page 6-7, Table D and Figure E).

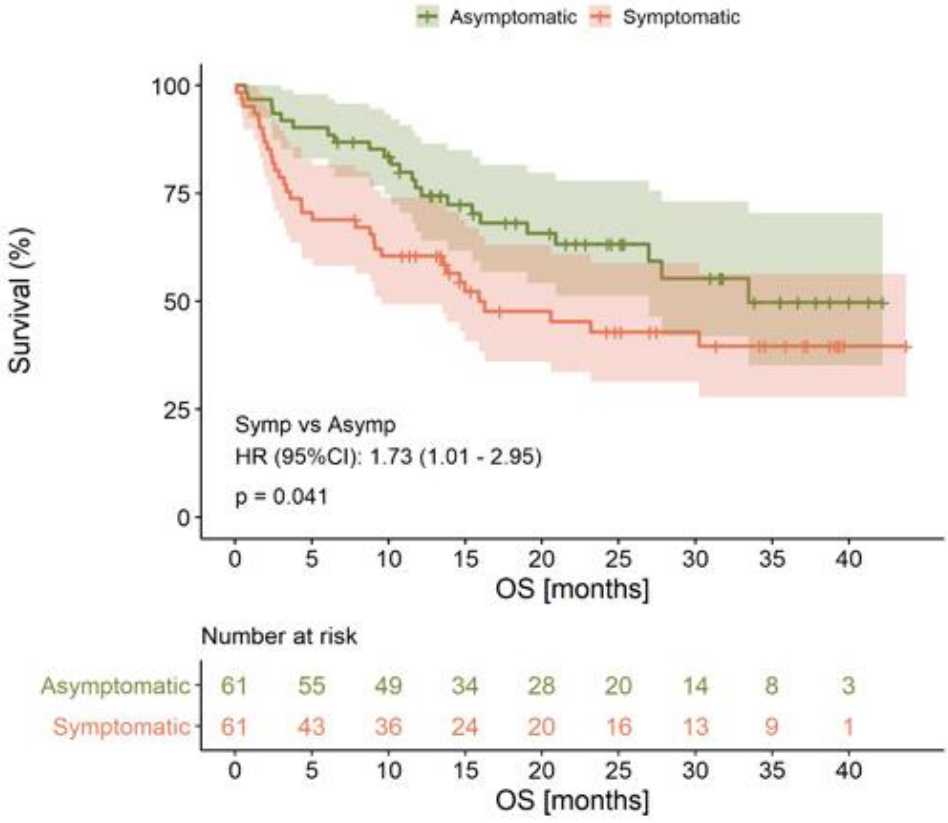
Table D: Characteristics of patients of the matched paired analysis for the 1:1 propensity score.

Variable	[ALL] N=122	Asymptomatic N=61	Symptomatic N=61	p.overall
Age, mean (SD)	70.4 (9.54)	70.3 (9.92)	70.4 (9.21)	0.992
Sex				0.799
Male, n (%)	104 (85.2%)	51 (83.6%)	53 (86.9%)	
Female, n (%)	18 (14.8%)	10 (16.4%)	8 (13.1%)	
Stage, n (%)				0.891

I	40 (32.8%)	21 (34.4%)	19 (31.1%)	
II	14 (11.5%)	8 (13.1%)	6 (9.84%)	
III	38 (31.1%)	18 (29.5%)	20 (32.8%)	
IV	30 (24.6%)	14 (23.0%)	16 (26.2%)	
ECOG, n (%)				1.000
0-1	104 (85.2%)	52 (85.2%)	52 (85.2%)	
>1	18 (14.8%)	9 (14.8%)	9 (14.8%)	

SD: Standard deviation. ECOG: Eastern Cooperative Oncology Group.

Figure E: Kaplan-Meier curve of the time between diagnosis and all-cause death between patients who were asymptomatic and symptomatic at diagnosis, from propensity score (PS) matching analysis.



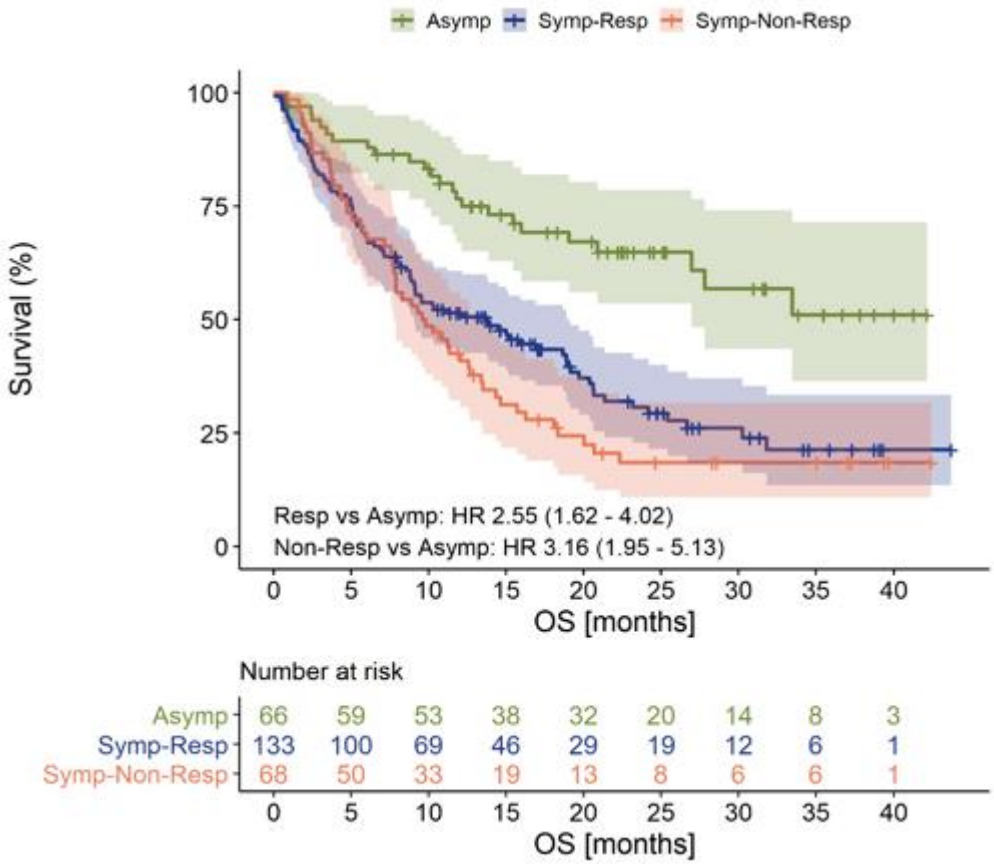
HR: Hazard Ratio. OS: Overall Survival. Symp: symptomatic patients. Asymp: asymptomatic patients.

C5: "*Did you observe any survival differences within the group of symptomatic patients? E. g. grouping respiratory vs. else?"*

R5: Based on the Reviewer's interesting comment, in line with comment C8 provided by Reviewer B, we have explored survival of symptomatic patients. We are providing a new figure called Figure B, where Kaplan Meier survival curves of patients categorized into three groups, asymptomatics, symptomatics with respiratory symptoms and symptomatics with non-respiratory symptoms, are presented. As you can observe, there is a significant difference between asymptomatic patients and the two categories of symptomatic ones (HR included in Figure B). However, no significant difference was observed between patients with respiratory and non-respiratory

symptoms (p=0.2). We are also attaching Figure B, which will be provided as supplementary material (supplemental material, Page 4, Figure B).

Figure B: Kaplan-Meier curve of the time between diagnosis and all-cause death between patients who were asymptomatic, symptomatic with respiratory symptoms and symptomatic with non-respiratory symptoms at diagnosis



Resp: symptomatic patients with respiratory symptoms. Asymp: asymptomatic patients. Non- Resp/

Symp-Non-Resp: symptomatic patients with non-respiratory symptoms. HR: Hazard Ratio. OS: Overall

Survival

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