PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan
AUTHORS	Tsai, Chang-Hung; Kung, Pei-Tseng; Kuo, Wei-Yin; Tsai, Wen-Chen

VERSION 1 – REVIEW

REVIEWER	Shalini Vinod Liverpool Hospital Australia
REVIEW RETURNED	15-Oct-2019

GENERAL COMMENTS	General comments This is an interesting topic of research addressed with a large health insurance database. There are grammatical errors and some spelling errors throughout the text. This would benefit from proof reading by someone proficient in English prior to future submission. Specific comments Methods The "Patient and Public involvement" statement is unnecessary. Simply that that "This is a retrospective study based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan." Why were patients who had palliative treatment in the first year excluded. Almost half of all NSCLC patients are stage IV at diagnosis with many needing palliative treatment at diagnosis. I find it surprising that only a minority of patients received palliative treatment within a year. Only 1934 patients received palliative treatment in the first year (and were excluded) but there are 24059 Stage IV NSCLC diagnosed. Are these patients receiving delayed palliative treatment or are they being treated "curatively" and if so this should be defined. What is the data accuracy of the registry? Need a statement about this in methods. Did treatment include prescription of oral targeted therapies? This could be a palliative treatment option in many patients. There is unnecessary duplication of information on variables in the statistical section which is provided immediately above. Table 2 Stage III and IV should be separated as Stage III is potentially curable and Stage IV not. It would make more sense to have column percentages in this table to show timelines per stage. Table 4

	Stage III and IV should be separately analysed as above. Discussion This section needs to be rewritten with reference to appropriate literature. Many relevant studies have not been referenced. It appears that many of the studies referenced are purely due to numbers of patients with the main point that this study has the largest no of patients for all stages of lung cancer for this research question. References 14 and 9 are irrelevant to the discussion. Reference 14 only appears to be inserted because of the number of patients. Reference 9 is on head and neck cancers not lung cancer. This study needs to be compared to other cancer registry studies looking at this research question, similarities and differences discussed, and reasons for discordant or concordant findings discussed. One useful reference which summarises useful references is Vinod SK et al. Lung Cancer 2017;112:16-24. Doubling times can be quite slow in early stage resectable NSCLC (Wilson DO et al, Am. J. Resp. Crit. Care Med.185 (2012) 85–89 and Mackintosh JA et al Respirol 19 (2014) 755–762) so a discussion as to why any time interval more than 7 days is associated with increased mortality in these patients is warranted. On the other hand Stage III NSCLC is known to grow rapidly (Mohammed N et al Int. J. Radiat. Oncol. Biol. Phys. 79 (2011) 466–472., Lin P et al Radiother. Oncol. 101 (2011)284–290, Everitt S et al Cancer 116 (2010) 5030–5037) so a greater effect of delays might be expected in these patients, however the current results group Stage III and IV so has not been analysed. References Reference 12 needs to be corrected.

REVIEWER	Daniel Raymond Cleveland Clinic Foundation Cleveland, Ohio, USA
REVIEW RETURNED	04-Nov-2019

GENERAL COMMENTS	I enjoyed reviewing the manuscript by Tsai and colleagues regarding treatment delay and impact on outcome for patients with NSCLC. The topic of time to treat is gaining significant interest and the authors provide an excellent discussion of the current literature in their discussion. I have the following comments: 1) One of the common themes in these studies is to use large databases to analyze this topic. The large size of the database is considered a strength, yet the investigators are limited to the data available in the database to perform their analysis. This becomes problematic when looking deeper into this topic. I do not think anyone would challenge the concept that sicker, more complex patients take longer to evaluate to determine candidacy for treatment. In the surgical population, one of the primary factors of concern is lung function. The CCI simply has a check for "COPD" which has essentially become a wastebasket term of little clinical value. What I suspect is that the patients with worse pulmonary function (who would naturally have worse long term survival) take longer to evaluate as they require additional testing (such as quantitative VQ scanning, cardiopulmonary exercise testing, etc.) To control for this, the authors need to include FEV1 and DLCO in

	the statistical analysis for surgical patients. If they cannot, they need to list this as a limitation in their discussion. Furthermore, the authors should track all pretreatment studies performed as a measure of the extent of evaluation done on each patient. Interestingly, all the additional physiologic eval is necessary for surgical patients only, thus this may explain why there is a more profound effect on the early stage patients as they point out in the study. 2) The stage I group creates a further challenge on at least two fronts. FIrst, how did the authors address surgical patients with TTT=0, meaning those who had their biopsy obtained in the operating room. This group would be included in the <7 day group and one should consider excluding them as this group tends to be healthy patients with small, peripheral cancers which would favor lower node positivity. Can the authors provide further characterization of the TTT=0 group? Were they healthier? Lower node (+) rates? Could this be a confounding variable? The authors should mention whether or not they included TTT=0 in their analysis as it has been handled in several different ways in the broader literature. Secondly, the stage I group also contains patients who were treated by variable means. Those patients treated with surgery, are by definition, healthier than those treated with SBRT(stereotactic radiosurgery) who are generally denied surgery for medical reasons. SBRT planning generally takes >1 week thus SBRT patients will not fall into the <1 week group, again creating a confounding problem as those patients with SBRT have more severe co-existing medical issues and thus a worse overall prognosis. Patients treated with SBRT are also inherently less well staged (no pathologic node analysis based on a surgical specimen) than surgical patients thus the survival may be impacted. Can the authors include treatment modality in their analysis of stage I patients? 3) Some of these confounding variables could be addressed by using disease free survival rather than crude survival. Do the authors have that data? If not, they should comment on the shortcomings of using crude survival in the discussion. 4) I believe they need to soften their conclusion statement. What they are demonstrating is an association, not proving cause and effect. They have not demonstrated that active interventions to shorten TTT results in improved survival.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

General comments

This is an interesting topic of research addressed with a large health insurance database. There are grammatical errors and some spelling errors throughout the text. This would benefit from proof reading by someone proficient in English prior to future submission.

Specific comments

Methods

The "Patient and Public involvement" statement is unnecessary. Simply that that "This is a retrospective study based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan."

Why were patients who had palliative treatment in the first year excluded.

Answer: The "Patient and Public involvement" statement is a requirement for all manuscripts submitted to BMJ Open.

It's an error about "palliative treatment in the first year". We have revised it as "palliative treatment at beginning". In Taiwan, palliative treatment is coded as special code in NHIRD. Non-small cell lung cancer patients with palliative treatment at beginning may be due to patients refusing further treatment or not receiving aggressive treatment. We excluded them for informal treatments. We have revised in page 7.

Almost half of all NSCLC patients are stage IV at diagnosis with many needing palliative treatment at diagnosis. I find it surprising that only a minority of patients received palliative treatment within a year. Only 1934 patients received palliative treatment in the first year (and were excluded) but there are 24059 Stage IV NSCLC diagnosed. Are these patients receiving delayed palliative treatment or are they being treated "curatively" and if so this should be defined.

What is the data accuracy of the registry? Need a statement about this in methods.

Answer: Thank you for your comments. The Taiwan Cancer Registry Database (TCRD) records data of all types of cancer diagnosed and treatments in patients in Taiwan. The completeness (97%) and data quality of the Cancer Registry Database has achieved at an excellent level.[9] The accuracy of NHIRD has been validated in previous studies.[10] We have revised in page 6 and page 7.

Did treatment include prescription of oral targeted therapies? This could be a palliative treatment option in many patients.

Answer: In Taiwan, oral targeted therapies have been used in lung cancer patients since 2011. We didn't include non-small cell lung cancer patients with oral targeted therapies in our study since we included newly diagnosed non-small cell lung cancer patients from 2004 to 2010. Thank you for your comments.

There is unnecessary duplication of information on variables in the statistical section which is provided immediately above.

Answer: Thank you for your valuable comments. We have revised in page 9.

Table 2:

Stage III and IV should be separated as Stage III is potentially curable and Stage IV not. It would make more sense to have column percentages in this table to show timelines per stage.

Answer: Thank you for your valuable comments. We have separated stage III and stage IV and conducted further analyses. The updated results were shown in page 14-15.

Table 4:

Stage III and IV should be separately analyzed as above.

Answer: We have separated stage III and stage IV and conducted further analyses. The updated results were shown in page 19-21.

Discussion

This section needs to be rewritten with reference to appropriate literature. Many relevant studies have not been referenced. It appears that many of the studies referenced are purely due to numbers of patients with the main point that this study has the largest no of patients for all stages of lung cancer for this research question. References 14 and 9 are irrelevant to the discussion. Reference 14 only appears to be inserted because of the number of patients. Reference 9 is on head and neck cancers not lung cancer.

Answer: Thank you for your valuable comments. We have rewritten with appropriate reference. We also have deleted references 14 and 9.

This study needs to be compared to other cancer registry studies looking at this research question, similarities and differences discussed, and reasons for discordant or concordant findings discussed. One useful reference which summarises useful references is Vinod SK et al. Lung Cancer 2017;112:16-24.

Answer: Thank you for your valuable comments. We have revised as manuscript in page 25.

Doubling times can be quite slow in early stage resectable NSCLC (Wilson DO et al, Am. J. Resp. Crit. Care Med.185 (2012) 85–89 and Mackintosh JA et al Respirol 19 (2014) 755–762) so a discussion as to why any time interval more than 7 days is associated with increased mortality in these patients is warranted.

Answer: Thank you for your valuable comments. We have added more discussion in page 27.

On the other hand Stage III NSCLC is known to grow rapidly (Mohammed N et al Int. J. Radiat. Oncol. Biol. Phys. 79 (2011) 466–472., Lin P et al Radiother. Oncol. 101 (2011)284–290, Everitt S et al Cancer 116 (2010) 5030–5037) so a greater effect of delays might be expected in these patients, however the current results group Stage III and IV so has not been analysed.

Answer: Thank you for your valuable comments. We have separated stage III and stage IV and conducted further analyses. We have added more discussion in page 27.

References:

Reference 12 needs to be corrected.

Answer: We have revised it shown in page 34.

Reviewer: 2

I enjoyed reviewing the manuscript by Tsai and colleagues regarding treatment delay and impact on outcome for patients with NSCLC. The topic of time to treat is gaining significant interest and the authors provide an excellent discussion of the current literature in their discussion. I have the following comments:

1) One of the common themes in these studies is to use large databases to analyze this topic. The large size of the database is considered a strength, yet the investigators are limited to the data available in the database to perform their analysis. This becomes problematic when looking deeper into this topic. I do not think anyone would challenge the concept that sicker, more complex patients take longer to evaluate to determine candidacy for treatment. In the surgical population, one of the primary factors of concern is lung function. The CCI simply has a check for "COPD" which has essentially become a wastebasket term of little clinical value. What I suspect is that the patients with worse pulmonary function (who would naturally have worse long term survival) take longer to evaluate as they require additional testing (such as quantitative VQ scanning, cardiopulmonary exercise testing, etc.) To control for this, the authors need to include FEV1 and DLCO in the statistical analysis for surgical patients. If they cannot, they need to list this as a limitation in their discussion.

Answer: Thank you for your valuable comments. We have listed lung function testing such as FEV1 and DLCO as limitation in page 29.

Furthermore, the authors should track all pretreatment studies performed as a measure of the extent of evaluation done on each patient. Interestingly, all the additional physiologic eval is necessary for surgical patients only, thus this may explain why there is a more profound effect on the early stage patients as they point out in the study.

Answer: Thank you for your valuable comments.

2) The stage I group creates a further challenge on at least two fronts. First, how did the authors address surgical patients with TTT=0, meaning those who had their biopsy obtained in the operating room. This group would be included in the <7 day group and one should consider excluding them as this group tends to be healthy patients with small, peripheral cancers which would favor lower node positivity. Can the authors provide further characterization of the TTT=0 group?

Answer: Thank you for your valuable comments. There were 7,363 cases with TTT=0 accounting for 17.14% of all patients in our study. We show the characterization of patients with TTT=0 in the following table A. We have added text related to characteristics of patients with TTT=0 in page 10-11.

Table A. The characteristics of patients with TTT=0

Variables		**TTT=0**	
		N	**%**
Total number		7,363	17.14
Gender			
	Female	3,258	44.25
	Male	4,105	55.75
Age			
	≦44	439	5.96
	45~54	1,209	16.42
	55~64	1,810	24.58
	65~74	2,082	28.28
	≧75	1,823	24.76
Mean age		64.67	
Monthly salary			
	Low-income	56	0.76
	≦17280	264	3.59
	17281~22800	3,527	47.90
	22801~28800	1,405	19.08
	28801~36300	534	7.25
	36301~45800	661	8.98
	≧45801	916	12.44
Urbanization of residence area			
	Level 1	2,115	28.72
	Level 2	2,149	29.19
	Level 3	1,105	15.01

	Level 4	1,102	14.97
	Level 5	206	2.80
	Level 6	358	4.86
	Level 7	328	4.45
CCI score			
	≤ 3	3,326	45.17
	4~6	1,364	18.53
	≥ 7	2,673	36.30
Other catastrophic Illness			
	No	7,128	96.81
	Yes	235	3.19
MDT care			
	No	6,438	87.44
	Yes	925	12.56
Hospital level			
	Medical centers	5,177	70.31
	Regional hospitals	2,061	27.99
	District hospitals	100	1.36
	Others	25	0.34
Hospital ownership			
	Public	3,230	43.87
	Private	4,133	56.13
Hospital services volume			
	Low	1,870	25.40
	Middle	3,453	46.90
	High	2,040	27.71
Treatment			
	Surgery	1,981	26.90
	Surgery + Radiotherapy	698	9.48

	Surgery + Chemotherapy	1,700	23.09
	Surgery + Radiotherapy +Chemotherapy	2,382	32.35
	Chemotherapy	203	2.76
	Surgery + Radiotherapy +Chemotherapy +Others	45	0.61
	Radiotherapy +Chemotherapy	256	3.48
	Radiotherapy	46	0.62
	Surgery + Others	1	0.01
	Surgery + Radiotherapy +Others	3	0.04
	Surgery + Chemotherapy + Others	2	0.03
	Radiotherapy +Chemotherapy+ Others	3	0.04

Were they healthier? Lower node (+) rates? Could this be a confounding variable? The authors should mention whether or not they included TTT=0 in their analysis as it has been handled in several different ways in the broader literature.

Answer: We included TTT=0 cases in the <7 days group in our study. We also show the treatment modality of patients with TTT=0 in the table A. We have added text related to characteristics of patients with TTT=0 in page 10-11.

Secondly, the stage I group also contains patients who were treated by variable means. Those patients treated with surgery, are by definition, healthier than those treated with SBRT(stereotactic radiosurgery) who are generally denied surgery for medical reasons. SBRT planning generally takes >1 week thus SBRT patients will not fall into the <1 week group, again creating a confounding problem as those patients with SBRT have more severe co-existing medical issues and thus a worse overall prognosis. Patients treated with SBRT are also inherently less well staged (no pathologic node analysis based on a surgical specimen) than surgical patients thus the survival may be impacted. Can the authors include treatment modality in their analysis of stage I patients?

Answer: Thank you for your comments. We have further analyzed the data related to treatment modality in stage I patients shown in the following table B.

Table B. Treatment modality in patients with stage I NSCLC

Treatment Modality	N	%
Surgery	2518	45.65%

Radiotherapy	142	2.57%
Chemotherapy	116	2.10%
Surgery + Radiotherapy	873	15.83%
Surgery + Chemotherapy	1017	18.44%
Surgery + Radiotherapy +Chemotherapy	765	13.87%
Surgery + Radiotherapy +Others	3	0.05%
Surgery + Radiotherapy +Chemotherapy +Others	15	0.27%
Radiotherapy +Chemotherapy	60	1.09%
Surgery + Others	1	0.02%
Radiotherapy +Others	2	0.04%
Radiotherapy +Chemotherapy+ Others	2	0.04%
Chemotherapy+ Others	2	0.04%

3) Some of these confounding variables could be addressed by using disease free survival rather than crude survival. Do the authors have that data? If not, they should comment on the shortcomings of using crude survival in the discussion.

Answer: Thank you for your valuable comments. We don't have disease free survival data due to data limitation. We have listed it as limitation in page 29.

4) I believe they need to soften their conclusion statement. What they are demonstrating is an association, not proving cause and effect. They have not demonstrated that active interventions to shorten TTT results in improved survival.

Answer: We have revised conclusion as "NSCLC patients with timeliness treatment in stage I and II have better survival rate than others" in page 30.

VERSION 2 – REVIEW

REVIEWER	Shalini Vinod Liverpool Hospital Australia
REVIEW RETURNED	21-Dec-2019

GENERAL COMMENTS	Thank you for answering my previous comments. It is extremely ambitious for lung cancer treatment to commence within 7 days of diagnosis considering the staging which is required eg PET scan, +/- brain imaging, possible EBUS for nodal

	staging, molecular subtyping of pathology. This group in the study (< 7 days to treatment) is skewed towards those whose cancer was diagnosed at the time or surgery as opposed to those who had an initial biopsy with treatment following. You may wish to add this point to the discussion. There are still some minor grammatical errors which need to be corrected prior to publication.

REVIEWER	Daniel Raymond Cleveland Clinic Cleveland, OH United States of America
REVIEW RETURNED	02-Jan-2020

GENERAL COMMENTS	Dr. Tsai and colleagues present a large series from the Taiwan Cancer Registry evaluating the impact of time to treat on survival for NSCLC. They report this as the largest cohort to date to evaluate this topic. I have the following questions and comments: The central weakness of this manuscript which is consistent with many of the publications of this topic is the use of a generalized database not intended to evaluate this problem. The large sample size does not eliminate a significant degree of bias which will impact the conclusions of this study. The challenge they, any many others face, is that they cannot address one of the central biases of this study, simply stated, sicker patients take longer to work up for surgery. They clearly demonstrate that sicker patients, based on the CCI, have a higher rate of mortality. So how can they say that the mortality is attributed to the disease and not the underlying health status? The dependency on the Charlson Comorbidity Index is problematic as the CCI is not meant to evaluate the severity of illness in patients undergoing lung resection. The only assessment of lung function in the CCI is the simple question, does the patient have COPD? The STS database recently removed the designation of COPD from the preoperative assessment given the lack of accuracy with which this diagnosis is distributed in clinical medicine. Rather, it now depends on the actual PFTs to determine lung disease. It is a fact that patients with poorer lung function require additional testing to determine candidacy for surgery. This testing, including six minute walk test, quantitative perfusion scans, cardiopulmonary exercise testing and consultation with pulmonary medicine takes time. Those patients may also consult with Radiation Oncology to discuss alternatives to surgery. All this takes time. Can the authors somehow address this conundrum? Do they have access to the additional testing/consultation performed before surgery and can that be included somehow in the analysis. Without this data, the most the authors can conclude is that there is a major association between time to treat and mortality. They certainly need to soften the conclusion statement in the abstract which implies a causative link that they cannot support with their data. They would further need to discuss this at length as a major weakness of this analysis in their discussion which is held by many large databases analyses of TTT that already exist in the literature. The extreme of this group, the TTT=0, may also be another avenue to evaluate this problem. Can the authors provide a detailed analysis of this group which tends to be a healthier population? What does that group look like with respect to CCI, comorbidities and mortality?

VERSION 2 – AUTHOR RESPONSE

Responses to reviewers' comments

Reviewer: 1
Reviewer Name: Shalini Vinod

It is extremely ambitious for lung cancer treatment to commence within 7 days of diagnosis considering the staging which is required eg PET scan, +/- brain imaging, possible EBUS for nodal staging, molecular subtyping of pathology. This group in the study (< 7 days to treatment) is skewed towards those whose cancer was diagnosed at the time or surgery as opposed to those who had an initial biopsy with treatment following. You may wish to add this point to the discussion.

Answer:

Thank you for your valuable comments. We have added this valuable point to our discussion as manuscript in page 27.

There are still some minor grammatical errors which need to be corrected prior to publication.
Answer:

Thank you for your suggestions.

Reviewer: 2
Reviewer Name: Daniel Raymond

Dr. Tsai and colleagues present a large series from the Taiwan Cancer Registry evaluating the impact of time to treat on survival for NSCLC. They report this as the largest cohort to date to evaluate this topic. I have the following questions and comments.

The central weakness of this manuscript which is consistent with many of the publications of this topic is the use of a generalized database not intended to evaluate this problem. The large sample size does not eliminate a significant degree of bias which will impact the conclusions of this study. The challenge they, any many others face, is that they cannot address one of the central biases of this study, simply stated, sicker patients take longer to work up for surgery. They clearly demonstrate that sicker patients, based on the CCI, have a higher rate of mortality. So how can they say that the mortality is attributed to the disease and not the underlying health status? The dependency on the Charlson Comorbidity Index is problematic as the CCI is not meant to evaluate the severity of illness in patients undergoing lung resection. The only assessment of lung function in the CCI is the simple question, does the patient have COPD? The STS database recently removed the designation of COPD from the preoperative assessment given the lack of accuracy with which this diagnosis is distributed in clinical medicine. Rather, it now depends on the actual PFTs to determine lung disease. It is a fact that patients with poorer lung function require additional testing to determine candidacy for surgery. This testing, including six minute walk test, quantitative perfusion scans, cardiopulmonary exercise testing and consultation with pulmonary medicine takes time. Those patients may also consult with Radiation Oncology to discuss alternatives to surgery. All this takes time. Can the authors somehow address this conundrum?

Answer:

Thank you for your valuable comments. We agree with reviewer's opinions. We used CCI and catastrophic illness to evaluate the comorbidity of the NSCLC patients in our study. It is a fact that patients with poorer lung function require additional testing to determine candidacy for surgery. This testing, including six minute walk test, quantitative perfusion scans, cardiopulmonary exercise testing and consultation with pulmonary medicine takes time and is not available in our study. We have revised text as manuscript in page 23.

Do they have access to the additional testing/consultation performed before surgery and can that be included somehow in the analysis.

Answer:

Thank you for your valuable comments. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is not available in our database. We have listed it as limitation in page 30.

Without this data, the most the authors can conclude is that there is a major association between time to treat and mortality. They certainly need to soften the conclusion statement in the abstract which implies a causative link that they cannot support with their data.

Answer:

Thank you for your valuable comments. We have revised our conclusion statement in the abstract as manuscript in page 4.

They would further need to discuss this at length as a major weakness of this analysis in their discussion which is held by many large databases analyses of TTT that already exist in the literature.
Answer:

Thank you for your valuable comments. We have revised text in the Discussion section as manuscript in page 23, and also listed it as limitation in page 30.

The extreme of this group, the **TTT=0**, may also be another avenue to evaluate this problem. Can the authors provide a detailed analysis of this group which tends to be a healthier population? What does that group look like with respect to CCI, comorbidities and mortality?

Answer:

Thank you for your valuable comments. We have further analyzed the subgroup with TTT =0. There were 7,363 cases with TTT=0 accounting for 17.14% of all patients in our study. There were 45.17% with CCI≤ 3 and 36.30% with CCI≥ 7, respectively, in this group with TTT=0. The mortality of this group with TTT=0 was 248.36 per thousand person-years. We show the mortality of other subgroups with TTT=0 in the following table A. The 5-year survival rate was 34.9% in this group with TTT=0. Table B shows that the survival rate in different stage of the patients with TTT=0. As in the comorbidity condition, there were 100% with lung fibrosis, 51.79% with neurological disease, 50.69%

with hypertension, 31.92% with chronic obstructive pulmonary disease (COPD), and 25.44% with diabetes mellitus (DM) of the group with TTT=0, which was shown in table C.

Table A. Mortality rate in different stage of patients with TTT=0 (1000 person-years)

Variables	Total	Stage I	Stage II	Stage III	Stage IV
Mortality	**248.36**	57.48	143.60	365.80	705.48
Gender					
Female	186.41	39.10	93.69	287.45	572.54
Male	311.91	79.28	188.52	417.89	848.15
Age					
≤ 44	170.21	25.71	114.65	184.39	552.01
45~54	170.68	30.46	115.67	246.90	523.97
55~64	177.76	37.42	83.09	301.66	526.26
65~74	253.55	64.95	168.73	391.35	729.16
≥75	487.34	135.02	276.71	610.00	1,134.72
Monthly salary					
Low-income	492.93	135.20	647.93	401.02	1,236.45
≤ 17280	266.04	40.62	161.70	377.62	751.11
17281~22800	293.06	77.06	173.14	401.31	748.73
22801~28800	266.55	47.80	152.33	394.83	768.78
28801~36300	203.92	47.09	110.10	288.86	592.98
36301~45800	168.19	39.26	95.53	246.93	552.42
≥45801	160.06	38.72	66.66	297.34	586.31
Urbanization					
Level 1	197.47	46.86	133.08	308.60	596.31
Level 2	233.33	58.84	134.66	348.71	673.20
Level 3	312.68	57.02	150.56	471.33	854.96
Level 4	288.07	66.88	171.40	387.63	819.07
Level 5	302.53	87.37	153.21	304.44	829.28
Level 6	355.67	88.31	146.39	417.77	853.77

Level 7	277.05	69.23	149.02	464.04	618.54
CCI score					
≤ 3	129.56	45.65	111.36	306.95	504.32
4~6	282.69	73.33	174.03	382.90	664.37
≥7	513.75	118.33	196.72	439.96	819.88
Illness					
No	245.79	56.26	140.16	359.92	699.29
Yes	349.35	101.91	249.68	650.83	982.88
MDT care					
No	242.27	56.98	138.95	363.42	719.39
Yes	296.98	62.72	186.37	379.71	626.45
Hospital level					
Level 1	219.49	54.50	143.93	335.76	679.98
Level 2	350.24	68.72	148.61	450.53	759.68
Level 3	260.71	93.18	120.20	421.92	735.43
Level 4	72.40	43.37	0.00	76.12	547.77
Hospital ownership					
Public	211.73	51.00	154.89	321.09	682.19
Private	281.63	64.59	137.56	400.86	722.20
Hospital services volume					
Low	360.15	78.44	164.24	492.21	801.11
Middle	241.24	62.73	141.44	352.37	724.12
High	184.32	38.67	131.04	281.84	584.93

Table B. Survival rate in different stage of patients with TTT=0

Duration	Total	Stage 1	Stage 2	Stage 3	Stage 4
6 months survival rate	0.805	0.982	0.935	0.786	0.642
1-year survival rate	0.678	0.959	0.852	0.619	0.441

2-year survival rate	0.529	0.907	0.721	0.424	0.230
3-year survival rate	0.441	0.848	0.648	0.306	0.132
4-year survival rate	0.389	0.795	0.578	0.241	0.095
5-year survival rate	**0.349**	0.740	0.498	0.209	0.069

Table C. Comorbidities of the lung cancer patients with TTT=0

Comorbidity	TTT=0 (N=7,363)	
	N	%
HIV / AIDS	1	0.01
Tubercukosis	758	10.29
Electrolyte / mineral imbalance	30	0.41
Anemia	388	5.27
Blood disorder	879	11.94
Demuntia	123	1.67
Neurologic disease	3,813	51.79
Congestive heart failure	438	5.95
Chronic obstructive pulmonary disease (COPD)	2,350	31.92
Pulmonary fibrosis	7,363	100.00
Gastrointestinal bleeding	187	2.54
Renal disease	560	7.61
Connective tissue disease	223	3.03
Hypertension	3,732	50.69
Diabetes mellitus (DM)	1,873	25.44
Cerebrovascular disease	1,001	13.60
Heart disease	1,474	20.02
Coronary artery disease	1,450	19.69

VERSION 3 – REVIEW

REVIEWER	Shalini Vinod Cancer Therapy Centre, Liverpool Hospital, Liverpool, NSW, Australia
REVIEW RETURNED	16-Feb-2020

GENERAL COMMENTS	Thank you for answering the queries.

REVIEWER	Daniel Raymond Cleveland Clinic United States of America
REVIEW RETURNED	11-Feb-2020

GENERAL COMMENTS	I appreciate the opportunity to review this manuscript for a second time and congratulate the authors on their fine work. I still believe, however, that the conclusions are overstated. What the authors have demonstrated is an association, not causation. The lack of preoperative variables that strongly impact the length of the preoperative evaluation period mean that further study is necessary prior to concluding that more timely treatment will impact survival. The authors final statement is an example of this. THey say, "NSCLC patients with timeliness treatment (needs correction) in stage I and II have better survival rate than others." This is true but they cannot say that is due to faster treatment or better health characteristics in the lung function. THis is well demonstrated by their TTT=0 population which is often the lowest comorbidity group and has the highest survival rate. I would suggest they change the tone of their conclusions to reflect the inability to better characterize their patient population. FOr example, the last paragraph of the discussion: "IN summary, this study identifies an association between time to treat and survival in lung cancer patients undergoing surgical intervention. Although causation is not definitive, efforts to diminish time to treat in the lung cancer patient would seem prudent while awaiting further study on the issue." THe last sentence of the conclusions: Treatment timeliness is associated with better survival rates in patients with NSCLC, particularly stage I and II. Strengths and limitations last bullet: Information on individual lifestyle and important health characteristics such as quantitative lung function and need for provocative cardiac testing are not available and may be significant factors determining the time to treat interval. Abstract Conclusions last sentence:

	We suggest that efforts should be made to minimize the interval from diagnosis to treatment while further study is ongoing to determine causation. The rest of the discussion needs to agree with this tone. The reality is that large numbers does not guarantee a lack of bias in a study. The lack of preoperative data introduces concern for bias that prevents conclusions stating causation.

VERSION 3 – AUTHOR RESPONSE

Responses to reviewer's comments:

Reviewer: 2

Please leave your comments for the authors below
I appreciate the opportunity to review this manuscript for a second time and congratulate the authors on their fine work. I still believe, however, that the conclusions are overstated. What the authors have demonstrated is an association, not causation. The lack of preoperative variables that strongly impact the length of the preoperative evaluation period mean that further study is necessary prior to concluding that more timely treatment will impact survival.

The authors final statement is an example of this. They say, "NSCLC patients with timeliness treatment (needs correction) in stage I and II have better survival rate than others." This is true but they cannot say that is due to faster treatment or better health characteristics in the lung function. This is well demonstrated by their TTT=0 population which is often the lowest comorbidity group and has the highest survival rate.
Answer:

Thank you for your valuable comments. We agree with reviewer's opinions. We have revised text as manuscript in page 30.

I would suggest they change the tone of their conclusions to reflect the inability to better characterize their patient population. For example, the last paragraph of the discussion:
"In summary, this study identifies an association between time to treat and survival in lung cancer patients undergoing surgical intervention. Although causation is not definitive, efforts to diminish time to treat in the lung cancer patient would seem prudent while awaiting further study on the issue."

Answer:

Thank you for your valuable comments. We have revised text as manuscript in page 29.

The last sentence of the conclusions:
Treatment timeliness is associated with better survival rates in patients with NSCLC, particularly stage I and II.

Answer:

Thank you for your valuable comments. We have revised text as manuscript in page 30.

Strengths and limitations last bullet:
Information on individual lifestyle and important health characteristics such as quantitative lung function and need for provocative cardiac testing are not available and may be significant factors determining the time to treat interval.

Answer:

Thank you for your valuable comments. We have revised text as manuscript in page 4.

Abstract Conclusions last sentence:
We suggest that efforts should be made to minimize the interval from diagnosis to treatment while further study is ongoing to determine causation.

Answer:

Thank you for your valuable comments. We have revised text as manuscript in page 3 and 4.

The rest of the discussion needs to agree with this tone. The reality is that large numbers does not guarantee a lack of bias in a study. The lack of preoperative data introduces concern for bias that prevents conclusions stating causation.
Answer:

Thank you for your valuable comments. We agree with reviewer's opinions. We have revised text as manuscript.

VERSION 4 – REVIEW

REVIEWER	Daniel Raymond Cleveland Clinic Cleveland, OH USA
REVIEW RETURNED	04-Mar-2020

GENERAL COMMENTS	I appreciate the chance to review this manuscript. I would make a few minor changes that again reflect the ability to determine causation. 1) In the discussion, the section on treatment <7 days is again overstating causation. There is a specific mention that decreasing TTT <7 days improves 5 year life expectancy. This is an overstatement. It is associated with an improvement in 5 year life expectancy. It is very likely that the TTT<7 days are the healthiest patients as they require no additional testing prior to proceeding with surgery. Causation needs to be determined with additional studies before a recommendation can be made to intentionally decrease TTT to < 7 days. This has huge implications for healthcare all over the world. This section should be modified to reflect an association, not state causation nor make definitive recommendations. 2) Starting on page 28, line 52 - same problem.

	"Therefore, this study found that timely treatment of stage I and II lung cancer patients has greater benefits. Therefore, we recommend that we should shorten the interval from diagnosis to treatment initiation especially in stage I and II lung cancer patients, thus decreasing the risk of death and improving prognosis. However, due to data limitation, we used crude survival instead of disease free survival." Would rewrite as "It appears the association between time to treatment and outcome is stronger with lower stage disease. This may have implications on resource allocation specifically addressing the TTT phenomenon. Further study, however, is necessary to better understand causation." 3) ON page 29, lines 50-56: "In addition, in stage III and stage IV patients, we recommend the addition of MDT care to decrease the risk of death and improve prognosis." Why is the recommendation only to apply MDT to patients in stage III and IV. Shouldn't that be the ideal for all patients, regardless of stage? Why is there no benefit for stage II patients who will need adjuvant chemotherapy?

VERSION 4 – AUTHOR RESPONSE

Responses to reviewer's comments:

Reviewer: 2

1) In the discussion, the section on treatment <7 days is again overstating causation. There is a specific mention that decreasing TTT <7 days improves 5 year life expectancy. This is an overstatement. It is associated with an improvement in 5 year life expectancy. It is very likely that the TTT<7 days are the healthiest patients as they require no additional testing prior to proceeding with surgery. Causation needs to be determined with additional studies before a recommendation can be made to intentionally decrease TTT to < 7 days. This has huge implications for healthcare all over the world. This section should be modified to reflect an association, not state causation nor make definitive recommendations.

Answer: Thank you for your valuable comments. We have revised text as manuscript in page 27.

2) Starting on page 28, line 52 - same problem.
"Therefore, this study found that timely treatment of stage I and II lung cancer patients has greater benefits. Therefore, we recommend that we should shorten the interval from diagnosis to treatment initiation especially in stage I and II lung cancer patients, thus decreasing the risk of death and improving prognosis. However, due to data limitation, we used crude survival instead of disease free survival."
Would rewrite as "It appears the association between time to treatment and outcome is stronger with lower stage disease. This may have implications on resource allocation specifically addressing the TTT phenomenon. Further study, however, is necessary to better understand causation."

Answer:

Thank you for your valuable comments. We agree with reviewer's opinions. We have revised text as manuscript in page 28-29.

3) ON page 29, lines 50-56:
"In addition, in stage III and stage IV patients, we recommend the addition of MDT care to decrease the risk of death and improve prognosis." Why is the recommendation only to apply MDT to patients in stage III and IV. Shouldn't that be the ideal for all patients, regardless of stage? Why is there no benefit for stage II patients who will need adjuvant chemotherapy?

Answer:

Thank you for your valuable comments. We have revised text as manuscript in page 29. “In addition, in patients with NSCLC, we recommend the addition of MDT care to decrease the risk of death and improve prognosis.