PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with cancer treatment delay: a protocol for a systematic review and meta-analysis
AUTHORS	Morrill, Kristin; Robles-Morales, Rogelio; Lopez-Pentecost, Melissa; Martínez Portilla, Raigam; Saleh, Ahlam; Skiba, Meghan; Riall, Taylor; Austin, Jessica; Hirschey, Rachel; Jacobs, Elizabeth; Spotleson, Lena; Hanna, Timothy

VERSION 1 – REVIEW

REVIEWER	Daniel Raymond Cleveland Clinic, Thoracic & Cardiovascular Surgery
REVIEW RETURNED	15-Mar-2022

GENERAL COMMENTS	I appreciate the opportunity to review the protocol for a potential meta-analysis of time to treat (TTT) studies. I have the following comments and questions: 1) The authors state that this is the first study of this type yet the first paper they cite is a meta-analysis of 34 studies. First of all, meta-analyses are not necessary for appropriate scientific study, they are simply a tool thus "filling a gap" in the literature is not a good reason. Rather they should explain why a meta-analysis is appropriate to analyze this topic. 2) My greatest concern with the protocol is turning the primary outcome into a dichotomous variable. They are basing this on the individual study's definition of delay in TTT but this determination is often an arbitrary breakpoint of a continuous variable, if stated at all in the study. It also implies we know what the appropriate TTT should be, which is completely false. I realize this makes it easier to generalize numerous studies with numerous pathologies but it is based on a false assumption. 2) I am also concerned that they are pooling different types of cancer when the relevant TTT delays may have dramatically different effects. Delay in treatment may in fact be more relevant for certain types of cancer and thus one risks a false conclusion by pooling cancer types. 3) Another concern is the variability that exists in the literature on this topic. There is no standard definition for TTT, how are they going to adjudicate this across studies? Some studies for instance assume time 0 is when the cancer is first imaged, others when the first biopsy is obtained. 4) There is also the difficult issue of how to handle TTT=0 which is common with certain types of cancer such as lung cancer (diagnostic wedge then lobe - often biased toward early stage and healthy individuals) and melanoma. Most studies simply ignore this very challenging issue. 5) A pervasive problem in the published TTT literature is the inadequate risk stratification of patients. The reality is that sicker

	patients take longer to work up for surgery as they requiring more testing and they also do poorer after surgery due to their comorbidities. The majority of studies on TTT are using large national databases which have very little in the way of appropriate detail to control for this. For example, many studies in lung cancer utilize databases that utilize the Charlson Comorbidity Index as the sole means of appropriate risk stratification. The CMI neglects essential variables such as lung spirometry, oxygen use, BMI, functional status that are vital to the appropriate risk stratification of lung cancer patients. In these studies a 50 yo who is wheel chair bound, morbidly obese, on supplemental O2 and with an FEV1 of 40% of predicted is no different than a 50 year old who runs daily, normal weight and an FEV1 of 100% predicted. Clearly the former is a much higher risk patient and will require considerably more testing that the latter, also a higher risk of postop events. This is just an example of the challenges faced in the published literature on this topic frankly due to a relative lack of understanding of the complexity by reviewers and the overuse of large national databases which are inadequately detailed to address the question at hand. (I am happy to discuss further with authors (Dan Raymond, raymond3@ccf.org). My group has an article in press addressing these topics - in our detailed analysis of TTT factors in early stage lung cancer, the top 5 determinants of TTT were 1. Surgeon 2. smoking history 3. Consult to Oncology before surgery 4. Hx of CVA 5. FEV1. Of those variables, most studies on lung cancer account for only one. My conclusion is large database studies on TTT are sadly flawed. Reviewers assume the CMI is appropriate for risk stratifying these patients and it is not.)

REVIEWER	Anne Hammer Aarhus University, Department of Clinical Medicine
REVIEW RETURNED	30-Mar-2022

GENERAL COMMENTS	Thanks for the invitation to review this protocol paper. The authors describe how they will conduct a systematic review on cancer treatment delay. The paper is very well written and the topic is important and clinically relevant. I applaude the inclusion of a patient advocate. With such a well written paper it's hard to make suggestions and comments, however, I have a few: 1. I suggest the authors should use the updated PRISMA guidelines from 2020 when conducting the review 2. Page 5, line 174. Do you mean systemic (and not systematic ?) 3. Page 7, line 261. What do you mean with cancer type. I assume cancer site is colon, breast, etc. Cancer type might be histologic subtype? Maybe be specific? 4. I am wondering why the authors have decided beforehand to use the random effects model before they have assessed the level of heterogeneity. As far as I know, the random effects model should be used when there is heterogeneity whereas the fixed-effect model should be used when there is not.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Daniel Raymond, Cleveland Clinic

1) The authors state that this is the first study of this type yet the first paper they cite is a meta-analysis of 34 studies. First of all, meta-analyses are not necessary for appropriate scientific study, they are simply a tool thus "filling a gap" in the literature is not a good reason. Rather they should explain why a meta-analysis is appropriate to analyze this topic.

Authors' Response:

Thank you for this comment. We wish to clarify that the subject of the proposed study is not focused on the effect of treatment delay on mortality as is the topic of the first paper cited by Hanna et al. (who is serving as senior author on the current protocol and review). The current systematic review and meta-analysis seeks to expand on the work by Hanna et al. by summarizing factors previously found to be associated with treatment delay, defined as the total time between a biopsy-proven diagnosis and initiation of first treatment, in the existing literature. This will inform efforts to support and triage recently diagnosed cancer patients based on risk of delay and inform strategies aimed at reducing treatment delay. We have revised the introduction paragraph to better articulate the purpose of the current systematic review and meta-analysis and how our findings will meaningfully expand upon the existing literature.

Below, we have highlighted revisions made to the manuscript text:

(Line 203) (Line numbers provided correspond to the “track changes” Word document)

While a small number of reviews have evaluated factors associated with treatment delays[17], no study, to our knowledge, has robustly quantified the relative impact of these factors on treatment delays in a meta-analysis. Calculating point estimates for the odds of time to treatment delay occurring within a specific time interval for patient, provider, and system-level factors has the potential to identify the most relevant factors contributing to treatment delay. This will inform efforts to manage and triage recently diagnosed cancer patients based on risk of delay as well as multi-level intervention strategies aimed at reducing treatment delay. Therefore, the purpose of this comprehensive meta-analysis and systematic review is to pool the odds ratios from previously identified factors on time to treatment for five common cancer sites (breast, lung, prostate, cervical, and colorectal cancer). To ensure the clinical relevance of our findings, we will present pooled effects for factors separately for each cancer site and further by first treatment modality (i.e. delays in breast cancer surgery after diagnosis will be evaluated independently from delays in neoadjuvant chemotherapy and radiotherapy for breast cancer). Additionally, the review will identify and discuss potential modifiable targets to guide future research and interventions aimed at reducing treatment delay. This robust synthesis is timely given the SARS-CoV-2 pandemic has exacerbated existing delays in cancer diagnosis and treatment.[18]

2) My greatest concern with the protocol is turning the primary outcome into a dichotomous variable. They are basing this on the individual study's definition of delay in TTT but this determination is often an arbitrary breakpoint of a continuous variable, if stated at all in the study. It also implies we know what the appropriate TTT should be, which is completely false. I realize this makes it easier to generalize numerous studies with numerous pathologies but it is based on a false assumption.

Authors' Response:

Thank you for this comment. We acknowledge the implicit limitations of studies that have categorized treatment delay as the outcome variable using a number of different benchmarks. We note that in prior meta-analyses of treatment delay and mortality, there is evidence to suggest a continuous log-linear association (Biagi et al., 2011; Raphael et al., 2016, Hanna et al., 2020). This implies that there may be no single 'right' cutoff, but rather a continued worsening impact of delay as time passes, rather than a discrete point defining a 'safe'vs 'unsafe' wait. It is acknowledged that the evidence supporting this relationship is not sufficiently robust to prove its application to all conditions.

After discussing the reviewer's concern among our co-authors, we have decided to change the primary outcome of the meta-analysis to acknowledge the varied cut-offs employed by different studies. ***Instead of defining the primary outcome as delay (yes/no) for each characteristic, the primary outcome will be the pooled unadjusted and adjusted odds of treatment delay according to specific cutoffs (15<30>44 days, 45<60>74 days, 75<90>114 days).*** We selected these 30-day time intervals as they are reflective of clinical practice patterns, are associated with clinically meaningingful associations between cancer treatment delay and survival, and have been used most consistently across studies investigating factors related to treatment delay across cancer sites (Cone et al., 2020; Bleicher et al., 2018; Heiden et al., 2021). In order to capture studies that have used a single treatment delay benchmark that was not a multiple of 30 days, we added +/- 15 days to each 30-day interval. For example, if an included study used a benchmark of 56 days to define delay or no delay, the study's outcomes would be summarized within the 45≤60>74 day time interval "bin".

For studies that report the relationship between a characteristic and a particular treatment delay interval as relative risk or as a beta-coefficient, we will convert these to an odds ratio so that we may summarize odds of treatment delay occurring within a specific time interval for a particular characteristic for each cancer site. Our goal is to be able to identify the odds of treatment being initiated after a discernable diagnosis within a specific treatment delay interval for each of the five cancers. This would allow us to answer the following question for example: *Compared to non-Hispanic Whites, what are the odds of time-to-treatment being within 30 days of diagnosis for a Hispanic women diagnosed with breast cancer whose first treatment was surgery?*

The secondary outcomes will be: 1) mean or median time-to-treatment for each cancer site according to first treatment (e.g., radiation vs. surgery) and 2) influence of identified risk factors or characteristics of the population on the pooled mean treatment delay for each cancer site (via meta-regression analyses).

We have chosen to retain the meta-regression as a secondary analysis as it permits inclusion of the broadest possible range of study types, reducing the risk of publication bias. It also provides an opportunity to determine the robustness of observed associations in the primary analysis when investigated via a different method.

References

Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305(22):2335-2342. doi:10.1001/jama.2011.749

Raphael MJ, Biagi JJ, Kong W, Mates M, Booth CM, Mackillop WJ. The relationship between time to initiation of adjuvant chemotherapy and survival in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2016;160(1):17-28. doi:10.1007/s10549-016-3960-3

Hanna T P, King W D, Thibodeau S, Jalink M, Paulin G A, Harvey-Jones E et al. Mortality due to cancer treatment delay: systematic review and meta-analysis BMJ 2020; 371 :m4087 doi:10.1136/bmj.m4087

Cone EB, Marchese M, Paciotti M, et al. Assessment of Time-to-Treatment Initiation and Survival in a Cohort of Patients With Common Cancers. JAMA Netw Open. 2020;3(12):e2030072. doi:10.1001/jamanetworkopen.2020.30072

Bleicher RJ. Timing and Delays in Breast Cancer Evaluation and Treatment. Ann Surg Oncol. 2018;25(10):2829-2838. doi:10.1245/s10434-018-6615-2

Heiden BT, Eaton DB, Engelhardt KE, et al. Analysis of Delayed Surgical Treatment and Oncologic Outcomes in Clinical Stage I Non–Small Cell Lung Cancer. JAMA Netw Open. 2021;4(5):e2111613. doi:10.1001/jamanetworkopen.2021.11613

Below we have highlighted revisions made to the manuscript text:

(Line 104 - Abstract)

The primary outcome of the meta-analysis will be the pooled adjusted and unadjusted odds of treatment delay for patient, disease, provider, and system-level factors defined according to specified time intervals. The secondary outcomes will be mean or median treatment delay for each cancer site according to first treatment and the influence of factors on the pooled mean treatment delay for each cancer site (via meta-regression analyses).

(Line 144)

Limitations:

- Wide treatment delay intervals will be used to pool findings from studies that employed various treatment delay cut-offs.

(Table 1)

O – Outcome

Inclusion Criteria:

Quantitative studies must have reported the outcome of treatment delay as odds ratio, risk ratio, relative risk, or beta-coefficient for each individual exposure

Exclusion Criteria:

We have no exclusion criteria based on outcome at this time

(Line 281)

To support meta-analysis, study sample size and effect size or measures of proportion specific to study factors (e.g., mean, median, standard deviation, interquartile range, unadjusted and adjusted hazard ratios, odds ratios, risk ratios, relative risk, and/or beta-coefficients and 95% confidence interval) will be extracted.

(Line 291)

The primary outcome of the meta-analysis will be the pooled adjusted and unadjusted odds of treatment delay defined according to specified intervals (15<30>44 days, 45<60>74 days, and/or

75<90>114 days). Factors associated with treatment delay will be quantified for individual patient, provider, and system-level factors for each cancer site and further stratified by first treatment (e.g. radiation vs. surgery). The secondary outcomes will be: 1) mean or median treatment delay for each cancer site according to first treatment (e.g., radiation vs. surgery) and 2) influence of identified risk factors or characteristics of the population on the pooled mean treatment delay for each cancer site (via meta-regression analyses).

(Line 321)

Data Synthesis

Extracted results from quantitative studies, including findings from mixed-methods studies, will be pooled in a meta-analysis. For studies that report the relationship between a characteristic and a particular treatment delay interval as relative risk or as a beta-coefficient, we will convert these to an odds ratio so that we may summarize odds of treatment delay occurring within a specific time interval for a particular characteristic for each cancer site. For the primary outcome, a generic meta-analysis by the inverse of the variance will be used for pooling the adjusted odds ratios from each study using random effects model as the preferred method despite the statistical heterogeneity. For the secondary outcomes, the pooled mean will be used as the pooled effect size by single mean analysis using random-effects modeling (weighting by inverse of variance) along with Clopper-Pearson “exact” method for calculation of confidence intervals. In case of a small number of studies (two or less), the fixed-effects model will be preferred over the random-effects model due to the poor precision of the random-effects for estimating between-study variance in such cases[25]. Between-study heterogeneity/variability will be assessed using the tau2, χ2 (Cochrane Q) and I2 statistics. Results will be assessed using forest plots and presented as proportions. Publication bias will be assessed by funnel plot in the case of more than 5 studies per outcome.

We have chosen to retain the meta-regression as a secondary analysis as it permits inclusion of the broadest possible range of study types, reducing the risk of publication bias. It also provides an opportunity to determine the robustness of observed associations in the primary analysis when investigated via a different method. Factors related to treatment delay will be pooled as proportions and mean or medians according to each study. To assess the influence of factors on treatment delay for each cancer site, a meta-regression will be performed when appropriate including all factors as predictors and the final pooled mean of delay for that cancer site as the main regression outcome. Coefficients with $p < 0.05$ will be considered statistically significant and will be considered to have an influence on the pooled result.

2) I am also concerned that they are pooling different types of cancer when the relevant TTT delays may have dramatically different effects. Delay in treatment may in fact be more relevant for certain types of cancer and thus one risks a false conclusion by pooling cancer types.

Authors' Response:

Thank-you. We share the reviewer’s concern, and wish to clarify that we will be pooling the odds of treatment delay occurring within a given interval for a range of patient, provider, and system-level characteristics ***for each of the five cancers individually, further stratified by treatment***. For example, we will examine studies that have assessed the relationship between factors on breast cancer treatment delay separately from those who have assessed the effects of factors on lung cancer treatment delay. As a sub-group analysis, we will additionally be evaluating factors (for each cancer site) separately by first treatment modality. For example, we will examine studies evaluating the odds of breast cancer surgery delay occurring within a given interval for a range of patient, provider, and system-level characteristics separately from studies evaluating the odds of breast cancer radiation occurring within a given interval for a range of characteristics. Our purpose in

separating our analyses further by first treatment is to identify whether the relationship between characteristics and treatment delay differs by first treatment for a particular cancer site. We have added a “Sub-Group Analysis” section under the Methods section of the manuscript text articulating this.

Below we have highlighted the revisions made to the manuscript text:

(Line 370)

Sub-Group Analysis

We will stratify our analyses conducted for each cancer site further by first treatment (e.g. radiation or surgery) to investigate whether the relationship between factors and treatment delay differs by first treatment.

3) Another concern is the variability that exists in the literature on this topic. There is no standard definition for TTT, how are they going to adjudicate this across studies? Some studies for instance assume time 0 is when the cancer is first imaged, others when the first biopsy is obtained.

Authors' Response:

As part of our eligibility criteria, we propose to only include studies that have defined T0 as the discernable diagnosis date based on biopsy. If studies do not use a discernable biopsy date to define T0, they will be excluded. Depending on the number of studies excluded for this reason, we may plan to conduct a sensitivity analysis including these studies to see if results change. We have included a “Sensitivity Analysis” section under the Methods section of the manuscript text articulating this.

Below we have highlighted revisions made to the manuscript text:

(Line 374)

Sensitivity Analysis

We will conduct a sensitivity analysis excluding studies not classified as high-quality based on the proposed risk of bias and quality assessment. We may conduct two separate additional sensitivity analyses (1) excluding studies that did not exclude patients with a time-to-treatment of 0 days and (2) excluding studies that did not use a discernable biopsy date as the date of diagnosis (for example, studies that defined the date of diagnosis as the date imaging was conducted).

4) There is also the difficult issue of how to handle TTT=0 which is common with certain types of cancer such as lung cancer (diagnostic wedge then lobe - often biased toward early stage and healthy individuals) and melanoma. Most studies simply ignore this very challenging issue.

Authors' Response:

Thank you for bringing up this issue. We acknowledge that these individuals with TTT=0 may be likely to have advanced cancer, and/or also likely being different, in many ways, than those with greater TTT. Additionally, the issue of unreliable diagnosis dates coded in large national databases such as the National Cancer Database is problematic (Yang et al., 2017); individuals who appear to be diagnosed on the same day they underwent surgical treatment would have underwent some type of indicator of diagnosis such as imaging before their surgery; however, this time interval is not usually reported. In a study using data from the Veterans Health Administration, the number of lung cancer patients with a reported TTT of 0 comprised nearly 30% of the patient population (Heiden et al., 2021). In our preliminary work, we found that many studies exclude patients with very low TTT.

However, ***to account for this issue, we will flag studies that do not exclude these very low TTT patients during screening.*** Based on the number of studies we exclude for this reason, we may plan to conduct a sensitivity analysis excluding these studies to see if results change.

References:

Heiden BT, Eaton DB, Engelhardt KE, et al. Analysis of Delayed Surgical Treatment and Oncologic Outcomes in Clinical Stage I Non–Small Cell Lung Cancer. JAMA Netw Open. 2021;4(5):e2111613. doi:10.1001/jamanetworkopen.2021.11613

Yang CJ, Wang H, Kumar A, et al. impact of timing of lobectomy on survival for clinical stage IA lung squamous cell carcinoma. Chest. 2017;152(6):1239-1250. doi:10.1016/j.chest.2017.07.032

Below we have highlighted revisions made to the manuscript text:

(Line 374)

Sensitivity Analysis

We will conduct a sensitivity analysis excluding studies not classified as high-quality based on the proposed risk of bias and quality assessment. We may conduct two separate additional sensitivity analyses (1) excluding studies that did not exclude patients with a time-to-treatment of 0 days and (2) excluding studies that did not use a discernable biopsy date as the date of diagnosis (for example, studies that defined the date of diagnosis as the date imaging was conducted).

5) A pervasive problem in the published TTT literature is the inadequate risk stratification of patients. The reality is that sicker patients take longer to work up for surgery as they requiring more testing and they also do poorer after surgery due to their comorbidities. The majority of studies on TTT are using large national databases which have very little in the way of appropriate detail to control for this. For example, many studies in lung cancer utilize databases that utilize the Charlson Comorbidity Index as the sole means of appropriate risk stratification. The CMI neglects essential variables such as lung spirometry, oxygen use, BMI, functional status that are vital to the appropriate risk stratification of lung cancer patients. In these studies a 50 yo who is wheel chair bound, morbidly obese, on supplemental O2 and with an FEV1 of 40% of predicted is no different than a 50 year old who runs daily, normal weight and an FEV1 of 100% predicted. Clearly the former is a much higher risk patient and will require considerably more testing that the latter, also a higher risk of postop events. This is just an example of the challenges faced in the published literature on this topic frankly due to a relative lack of understanding of the complexity by reviewers and the overuse of large national databases which are inadequately detailed to address the question at hand.

Authors' Response:

Thank you for citing this important limitation of studies in the existing literature. We acknowledge that most data sources used in TTT studies lack many relevant clinical indicators as well as information on individual-level social determinants of health and health behaviors that can provide a more nuanced understanding of why patients experience longer time-to-treatment and who is most at risk. We also acknowledge that the Charlson Comorbidity Index is a blunt instrument and risk stratification is imperfect and will likely lead to residual confounding in analyses identifying factors associated with greater time-to-treatment. However, many of the studies do include sociodemographic variables that are related to risk of death and comorbidity. As part of our data extraction, ***we plan to extract, summarize, and compare the types of information we obtain from different data sources and study designs to inform future efforts to evaluate patient, provider, and system-level characteristics associated with greater time-to-treatment***. Further, given the limitations of large national data sources, electronic medical record data, and cancer registry data in the breadth of

individual-level patient information collected, we made the decision ***to include qualitative reports and proposed to tabulate and summarize salient themes (usually from the perspective of the patient or provider) for why patients experience greater time-to-treatment.*** Including both quantitative and qualitative reports acknowledge the limitations and strengths of both types of approaches and will enrich our understanding of why greater time-to-treatment occurs among a particular patient population. Lastly, we plan to conduct a sensitivity analysis including only high-quality research articles which takes into consideration whether studies controlled for several variables previously identified to be associated with treatment delay. We have revised the manuscript text to include the proposed sensitivity analysis as outlined below:

Below we have highlighted revisions made to the manuscript text:

(Line 231)

We have chosen to include both quantitative and qualitative reports to acknowledge the limitations and strengths of both types of approaches and enrich our understanding of why greater time-to-treatment occurs among a particular patient population. Additionally, salient themes identified in the included qualitive studies will provide a lens by which to attempt to contextualize and make sense of the study's quantitative findings.

Reviewer: 2
Dr. Anne Hammer, Aarhus University, Gødstrup Hospital

1. I suggest the authors should use the updated PRISMA guidelines from 2020 when conducting the review

Authors' Response:

Thank you for this suggestion. We plan to use PRISMA 2020 guidelines to facilitate reporting in the final review manuscript. Given PRISMA 2020 is not intended to inform the reporting of systematic review protocols (Page et al., 2021), we have used the recommended PRISMA-P 2015 statement.

Reference:

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews BMJ 2021; 372 :n71 doi:10.1136/bmj.n71

2. Page 5, line 174. Do you mean systemic (and not systematic ?)

Authors' Response:

Thank you for catching this error. We have revised the sentence as demonstrated with the below highlighted text:

(Line 176)

For surgery, each 4-week delay was associated with a 6-8% increase in risk of death with even greater risk for radiotherapy and systemic therapy options.[1]

3. Page 7, line 261. What do you mean with cancer type. I assume cancer site is colon, breast, etc. Cancer type might be histologic subtype? Maybe be specific?

Authors' Response:

We have removed the phrase, "type of cancer" and have clarified information to be extracted in the following paragraph:

(Line 274)

Additionally, information/data related to the study's population, setting, and outcome(s) will be extracted including the following: study design, study period, cancer site, treatment modality (e.g. surgery, neoadjuvant chemotherapy), participant inclusion and exclusion criteria, population description (e.g. age, sex, race/ethnicity, tumor characteristics), study definition of delay and/or time-to-treatment intervals (e.g. 15<30>44 days, 45<60>74 days, 75<90>114 days), mean or median time from diagnosis to first treatment, factors evaluated in relation to treatment delays, study results, and information related to methodological quality.

4. I am wondering why the authors have decided beforehand to use the random effects model before they have assessed the level of heterogeneity. As far as I know, the random effects model should be used when there is heterogeneity whereas the fixed-effect model should be used when there is not.

Thank you for this comment. We wish to clarify that the selection of fixed or random effects models is best made based on the evaluation of whether study effect sizes are drawn from a distribution or from a single population. In the case of multiple published studies with varying patient, system and disease factors, the random effects framework fits best (Borenstein et al). Notably, in practice, results from random effects and fixed effects models will converge when there is limited heterogeneity.

VERSION 2 – REVIEW

REVIEWER	Daniel Raymond Cleveland Clinic, Thoracic & Cardiovascular Surgery
REVIEW RETURNED	25-May-2022

GENERAL COMMENTS	I appreciate the authors efforts to address the reviewer comments. They have done an exemplary job of doing so in a logical and meaningful way.