JTD JOURNAL OF THORACIC DISEASE
A PEER-REVIEWED, OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN THORACIC DISEASES
IMPACT FACTOR 2.895

Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-1217

Reviewer A

Comment 1: The setting and the faculty of each ICU should be mentioned.

Reply 1: Thank you for your suggestion. The relevant information has add as a supplement.

Changes in the text: Please check supplement “The information of each ICU”.

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The Information of Each ICU

NO.	The name of institute	The type of institute	The type of ICU	The number of beds in ICU
1	The First Affiliated Hospital of Guangzhou Medical University	Teaching hospital	General	37
2	Guangdong Provincial People's Hospital	Teaching hospital	Surgical	33
3	Huizhou First Hospital	Teaching hospital	General	15
4	The First Affiliated Hospital of Shantou University Medical College	Teaching hospital	General	20
5	The First Affiliated Hospital of Guangdong Pharmaceutical University	Teaching hospital	General	10
6	Shunde Hospital of Southern Medical University	Teaching hospital	General	19
7	The First Affiliated Hospital, Sun Yat-sen University	Teaching hospital	Surgical	18
8	Guangdong Hospital of Traditional Chinese Medicine,Zhuhai	Teaching hospital	General	12
9	ShunDe Hospital GuangZhou University of Chinese Medicine （ ShunDe District Hospital	Teaching hospital	General	14

Comment 2: The weaning protocol in each ICU should be mentioned

Reply 2: Thank you for your suggestion. The weaning protocol in each ICU will be supplied as a supplement named “weaning questionnaire”.

Changes in the text: Please check supplement “weaning questionnaire”

Comment 3: The prophylactic use of HFNC or NIV post-extubation could be recorded.

Reply 3: Thank you for your suggestion. We agree with you, this record has already set in our “weaning questionnaire”, for the content is limited, “weaning questionnaire” will offer as a supplement.

Changes in the text: Supplement “weaning questionnaire” page 13-14, the highlight part.

撤机后第1天序贯方式（不定项，多选视为组合）ventilatory support methods after weaning at day 1	☐无 ☐氧疗（鼻导管吸氧、鼻罩吸氧） 每日持续时间：_____（例：24hqd，8hqn） ☐ NIV 参数：☐BiPAP，IPAP____cmH2O，EPAP____cmH2O,FiO2____% 每日持续时间：_____（例：2htid，4h bid） ☐CPAP，CPAP____cmH2O, FiO2____% 每日持续时间：_____（例：2htid，4h bid） ☐HFNC 参数：流量____L/min， FiO2____% 每日持续时间：_____（例：2htid，4h bid） ☐no ☐Oxygen therapy (nasal duct oxygen, nasal mask oxygen) Daily duration: _____ (e.g. 24h qd, 8h qn) ☐ NIV Parameters: ☐BiPAP, IPAP____cmH2O, EPAP____cmH2O,FiO2____% Daily duration: _____ (e.g. 2h TID, 4h bid) ☐CPAP, CPAP____cmH2O FiO2____ % Daily duration: _____ (e.g. 2h TID, 4h bid) ☐ HFNC Parameters: Traffic ____L/min, FiO2____% Daily duration: _____ (e.g. 2h TID, 4h bid)

撤机后第2天序贯方式（不定项，多选视为组合） ventilatory support methods after weaning at day 2	☐无 ☐氧疗（鼻导管吸氧、鼻罩吸氧） 每日持续时间：_____（例：24hqd，8hqn） ☐ NIV 参数：☐BiPAP，IPAP____cmH2O，EPAP____cmH2O,FiO2____% 每日持续时间：_____（例：2htid，4h bid） ☐CPAP，CPAP____cmH2O,FiO2____% 每日持续时间：_____（例：2htid，4hbid） ☐HFNC 参数：流量____L/min ,FiO2____% 每日持续时间：_____（例：2htid，4h bid） ☐no ☐Oxygen therapy (nasal duct oxygen, nasal mask oxygen) Daily duration: _____ (e.g. 24h qd, 8h qn) ☐ NIV Parameters: ☐BiPAP, IPAP____cmH2O, EPAP____cmH2O,FiO2____% Daily duration: _____ (e.g. 2h TID, 4h bid) ☐CPAP, CPAP____cmH2O FiO2____ % Daily duration: _____ (e.g. 2h TID, 4h bid) ☐ HFNC Parameters: Traffic ____L/min, FiO2____% Daily duration: _____ (e.g. 2h TID, 4h bid)

Reviewer B

Comment 1: Please list the complete list of 10 hospitals included in this study in the supplement. May consider to add a map of 10 hospitals locations.

Reply 1: Thank you for your suggestion.

Changes in the text:we have listed the complete list of 17 hospitals included in this study in the supplement. And we have added a map as well. Hospitals are located in Guangdong province in China. Please refer to supplement Appendix Table 1 and AppendixFigure 1.

Comment 2:Page 4. Methods-- Patient screening. For the exclusion criteria, please clarify the “without the possibility for weaning” and list the conditions clearly that will be classified as “terminal stage of disease”.

Reply 2: Thank you for your advice.The main situation “without the possibility for weaning” in our exclusion criteria is defined as： （I） dyscrasia caused by advanced malignancy diagnosed by specialists;（II）patients with neuromuscular disease leading to spontaneous ventilation damage. (e.g., motor neuron disease).
Changes in the text: Page 4 128-132.The exclusion criteria are (I)Patients under 18 years of age ; （II）dyscrasia caused by advanced malignancy diagnosed by specialist;（III）patients with neuromuscular disease leading to spontaneous ventilation damage (e.g., motor neuron disease) ;(IV) COVID-19 patients were excluded from the study.

Comment 3: Page 5. Methods--Weaning screening. Please add reference for the contents of weaning screening.
Reply 3: Thank you for your suggestion.
Changes in the text: We add reference:
no. 17 “MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, Hess D, Hubmayer RD, Scheinhorn DJ; American College of Chest Physicians; American Association for Respiratory Care; American College of Critical Care Medicine. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest. 2001 Dec;120(6 Suppl):375S-95S. doi: 10.1378/chest.120.6_suppl.375s. PMID: 11742959 (See Page 5, line 171)”.

Comment 4: Page 6. Methods--Weaning screening. Please add P0.1 in the screening items and add reference because P0.1 is described a lot in the discussion.
Reply 4: Thank you for your suggestion, for the content limit, we list this index in supplement “weaning questionnaire”.
Changes in the text: See supplement “weaning questionnaire” (Page7 the highlight part).

呼吸力学指标 respiratory mechanics indices	☐有yes ☐无no （如果选择“有”，请回答以下问题If “yes”, please answer the following questions） 呼吸浅快指数RSBI：_____(次/min)/L NIF maximum negative inspiratory pressure（cmH2O）：_____ P0.1（cmH2O）：_____ 其他other：_____（单位unit：_____）

Comment 5: Page 6. Methods--Weaning processing. Please add reference for the contents of “Weaning method (SBT or not)”.
Reply 5: Thank you for your suggestion.
Changes in the text: We add reference no.22-23. (Page 5, line 172)

no. 18. Santos Pellegrini JA, Boniatti MM, Boniatti VC, Zigiotto C, Viana MV, Nedel WL, Marques LDS, Dos Santos MC, de Almeida CB, Dal' Pizzol CP, Ziegelmann PK, Rios Vieira SR. Pressure-support ventilation or T-piece spontaneous breathing trials for patients with chronic obstructive pulmonary disease - A randomized controlled trial. PLoS One. 2018 Aug 23;13(8):e0202404. doi: 10.1371/journal.pone.0202404. PMID: 30138422; PMCID: PMC6107186".

no.19.Thille AW, Coudroy R, Gacouin A, Ehrmann S, Contou D, Dangers L, Romen A, Guitton C, Lacave G, Quenot JP, Lacombe B, Pradel G, Terzi N, Prat G, Labro G, Reignier J, Beduneau G, Dellamonica J, Nay MA, Rouze A, Delbove A, Sedillot N, Mira JP, Bourenne J, Lautrette A, Argaud L, Levrat Q, Devaquet J, Vivier E, Azais MA, Leroy C, Dres M, Robert R, Ragot S, Frat JP; REVA research network. T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high risk of reintubation: protocol for a multicentre, randomised controlled trial (TIP-EX). BMJ Open. 2020 Nov 24;10(11):e042619. doi: 10.1136/bmjopen-2020-042619. PMID: 33234658; PMCID: PMC7689072).

Comment 6: Page 7. Methods-- Primary outcomes. Please clarify the definition of weaning success in this study, eg days of liberation. Also add reference to weaning success.

Reply 6: Thank you for your suggestion.

Changes in the text:We have add this part in Pgae7, line 213-218, and reference no 33-34.Weaning Success and Failure Definitions:According to the definition provided by the 2007 InternationalTask Force, weaning success is establishedwhen a patient who has just been extubated does not requireventilatory support for at least 48 h after the extubationprocedure. Accordingly, weaning failure is characterizedby: (1) an unsuccessful SBT, (2) reintubation/recannulation and/or the resumption of MV, or (3) death within 48 hours of extubation.

No.33Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. Eur Respir J. 2007 May;29(5):1033-56. doi: 10.1183/09031936.00010206. PMID: 17470624.

No. 34Thille, Arnaud W. MD, PhD1,2,3; Boissier, Florence MD3; Ben Ghezala, Hassen MD3; Razazi, Keyvan MD3; Mekontso-Dessap, Armand MD, PhD3; Brun-Buisson, Christian MD3 Risk Factors for and Prediction by Caregivers of ExtubationFailure in ICU Patients, Critical Care Medicine: March 2015 - Volume 43 - Issue 3 - p 613-620doi: 10.1097/CCM.0000000000000748

Comment 7: Page 8. Methods—statistics. The statistics section is too long for the protocol. Please extensively modified statistics into concise and relevant issues for this study.

Reply 7: Thanks for your suggestion. This manuscript has been revised accordingly.

Comment 8: Page 10. Discussion. Please discuss the role of RSBI in weaning screening and may compare with P0.1. RSBI seems to be used more widely than P0.1 in clinical practice.

Reply 8: Thank you for your suggestion. We have added the role of RSBI in weaning screening in discussion.

Changes in the text: See page 9, line 287-300. As we knew, the rapid shallow breathing index (RSBI) was widely used by clinicians to support decision-making during weaning and topredict the likelihood of successful weaning frominvasive mechanical ventilation (IMV)[43]. The earliest study conducted by Yang and Tobin proposed thatan RSBI of < 105 (rounded < 100 in somestudies) measured using a Wright's spirometer andwithout ventilator support was identified as a thresholdless than which extubation was more likely to besuccessful (sensitivity, 0.97; specificity, 0.64) for mostpatients[44]. This threshold of RSBI is still accepted by most clinicians in nowadays. Recently, another major meta-analysis has pointed that across 48 studies (10,946 patients), theRSBI showed not perfect enough for predicting extubationsuccess (sensitivity, 0.83; specificity, 0.58), with no credible subgroup effects based onthresholds, measurement techniques, or patientcharacteristics.[45]The writer considersRSBI is a simple measure ofrespiratory mechanics. Patients in different ICUs (e.g., medical, surgical,cardiovascular, and neurologic) may have variablerespiratory drive and clinical indications for ongoingIMV. These differences may precludeclinicians from using the RSBI in directing weaning from IMV.

Reference:

43.Burns KEA, Raptis S, Nisenbaum R, Rizvi L, Jones A, Bakshi J, Tan W, Meret A, Cook DJ, Lellouche F, Epstein SK, Gattas D, Kapadia FN, Villar J, Brochard L, Lessard MR, Meade MO. International Practice Variation in Weaning Critically Ill Adults from Invasive Mechanical Ventilation. Ann Am Thorac Soc. 2018 Apr;15(4):494-502. doi: 10.1513/AnnalsATS.201705-410OC. Erratum in: Ann Am Thorac Soc. 2018 Jul;15(7):894. PMID: 29509509.

44.Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med. 1991 May 23;324(21):1445-50. doi: 10.1056/NEJM199105233242101. PMID: 2023603.

45.Trivedi V, Chaudhuri D, Jinah R, Piticaru J, Agarwal A, Liu K, McArthur E, Sklar MC, Friedrich JO, Rochwerg B, Burns KEA. The Usefulness of the Rapid Shallow Breathing Index in Predicting Successful Extubation: A Systematic Review and Meta-analysis. Chest. 2021 Jun 26:S0012-3692(21)01257-5. doi: 10.1016/j.chest.2021.06.030. Epub ahead of print. PMID: 34181953.

Comment 9: Page 10. Discussion. Please provide descriptions and summary of current ICU/critical care in China. Although authors claim that there is no data for clinical application of weaning in China, there are some publications about weaning and ICU epidemiology of China. Please review current publications or government data and write a summary in the discussion. ICU specialists of the world will be interested in the summary of China critical epidemiology.

Reply 9: Thank you for your suggestion. Previous studies showed that simple, difficult and prolonged weaning could occur in 58%, 29% and 13% patients, respectively. Reference: Pu L, Zhu B, Jiang L, Du B, Zhu X, Li A, Li G, He Z, Chen

W, Ma P, Jia J, Xu Y, Zhou J, Qin L, Zhan Q, Li W, Jiang Q, Wang M, Lou R, Xi X. Weaning critically ill patients from mechanical ventilation: A prospective cohort study. J Crit Care. 2015 Aug;30(4):862.e7-13. doi: 10.1016/j.jcrc.2015.04.001. Epub 2015 Apr 16. PMID: 25957496.
Changes in the text: See page10, line 349-350.

Reviewer C

Comment 1: I read this paper with great interest! Extubation failure is an ongoing clinical challenge. In an attempt to liberate patients from the ventilator, some patients undergo premature extubation leading to extubation failure and this article provides a protocol they will use to conduct a retrospective study to explore the variations in weaning strategies across 17 ICUs in China. However, my major concern with this manuscript is that it provides simple details regarding the study protocol which included no novel methodology or strategy. Additionally, the study period is listed as retrospective (October 2020 and February 2021) but the study flow diagram implies that the study was done prospectively requiring charge clinicians to fill out the study form. I would be highly interested in reading the results on this study once published but at this stage, I believe, this manuscript adds no real value in advancing science.

Reply 1: Thank you for your great encouragement andapproval. The study flow diagram may express not exactly, that implies a wrong information, for this part we will correct it immediately. As this study is retrospective research, it may not bring some novel methodology or strategy for this time. Through this retrospective study, we hope to have a better understanding of the weaning situation of most centers in China. Base on this study, we will buildupaweaningmodelwhichisan integrative weaning index to predict weaning from mechanical ventilation.
Changes in the text: Page 4,line 122.The study flow diagram has been removed.

Reviewer D

Major issues:

Comment 1）a.How is the assessing clinician chosen? How does that person acquire the requested data?

Reply 1) a: Thank you for your question. The assessing cliniciansare each center ICU doctors not for certain, the form is filled by the secondclinician for certain in each center who was well trained before the study. A meeting was held with all centers to discuss the study items. Electronic medical record system or other electronic medical care system of each center was explored before study. All systems from each center met the study requirements. The requested data wereacquired in an electronic medical record system or other electronic medical care system of each center.
Changes in the text: See Page4,line 134-140.

Comment 1）b. Which lab and vitals values are used? Best in last 24 hours? Worst in last 48 hours? Most recent? It is unclear from the manuscript.

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Reply 1) b: Thank you for your advice. We show the requirements for filling the form included:Fill the index with the ward round result in the weaning day morning. Fill in the best data of biochemical experiment or examination performed 24-48 hours before or after weaning. (See page 5, line 167-170)

Changes in the text: See page 5, line 167-170.

Comment 1）c. Is a cough strength assessment done on every patient? These methods of assessment are profoundly different. Where are cutoffs being applied?

Reply 1) c: Thank you for your question. A cough strength assessment isn't done on every patient whether done or not is decided by their weaning evaluators, so we have set a "no" choice in the "weaning questionnaire" (please see details in supplement material). As you mentioned"these methods of assessment are profoundly different", we agree with you, but these methods are available in teaching books or some other authoritative research, we think these methods are currently accepted for cough strength assessment, even though they are not perfect.

Changes in the text: supplement "weaning questionnaire" page 8, the highlight part.

咳嗽能力评估 Cough strength assessment	?有yes ?无no （如果选择“有”，请回答以下问题If “yes”, please answer the following questions） 评估方法evaluation methods： ?方法1 Method 1 ：监测咳嗽时呼气峰流速（PEF） Spirometry – A spirometer (specifically designed for mechanical ventilators) is inserted into the ventilator circuit and the patient is then instructed to cough. The PEF during the cough is measured. Most experts use a cutoff of PEF ≤60 L/min since this indicates a high likelihood of failure. Patients with a PEF ≤60 L/min are five times more likely to require reintubation than patients with a PEF >60 L/min ?方法2Method 2：将气管插管从呼吸机管路上卸下，然后将一张卡片，如索引卡片，置于气管插管近端大约1-2cm的地方，然后让患者咳嗽 Index card – The endotracheal tube (ETT) is detached from the ventilator circuit and a card (eg, an index card) is held approximately 1 to 2 cm from the proximal end of the ETT. The patient is then instructed to cough. A patient who is unable to moisten the card with 3 to 4 coughs is three times more likely to fail extubation than a patient who can moisten the card. ?方法3 Method 3：观察咳嗽情况，凭医生经验决定 Cough strength is assessed informally during deep (endotracheal) suctioning at the bedside depending on clinicians’ experience. 评估结果 Evaluation result（根据选择方法勾选对应的结果）： 方法1Method 1：?PEF≤60L/min ?PEF>60L/min 方法2 Method 2：?3-4次咳嗽能够将卡片弄湿moisten the card with 3 to 4 coughs ?5次或以上咳嗽将卡片弄湿moisten the card with up to 5 coughs 方法3 Method 3：?正常Normal ?强 Strong ?弱 Weak

Comment 1）d. How is prognosis assessed?

Reply 1) d: Thank you for your question. The prognosis is mainly assessed by two parts. Part 1 is the weaning success rate. Part 2 is the secondary outcome, such as ventilator-free days within 28 days, reintubation within 48 hours after extubating, need for tracheostomy during weaning process after first SBT, length of stay in ICU and hospital, mortality in ICU, hospital (post-ICU), type of hospital discharge. Changes in the text: Page 7-8, line206-226.

Comment 1）e. How are cost values assessed? This alone is a major undertaking.

Reply 1) e: Thank you for your question.For this is a retrospective study, we can only acquirethe cost valueinformationthroughtheelectronic medical record system after the patient discharge. We agree with you that this alone is a major undertaking. We will conduct a prospectivestudybased on this study.

Changes in the text: details please in supplement “weaning questionnaire” page 17, the last line.

费用 Fee	ICU费用： ?<10万?>10万≤100万?≥100万 总住院费用：?≤10万?>10万至≤100万?>100万 ICU cost： ?< 100,000 ?> 100,000 ≤1,000,000 ?≥ 1,000,000 Total hospitalization expenses： ?≤ 100,000 ?> 100,000 to ≤ 1,000,000 ?> 1,000,000

2) The primary endpoints appear to be\:
a. Weaning success rate, clustered by center
b. Univariate analysis with the strongest association with successful weaning
c. A multivariate model of predicting weaning.
The issue with this, however, is that there is no plan for assessing the model (a validation and derivation cohort would be usual), nor is there clear assessment of what variable will be used to optimize it (AUROC? Specificity?). Similarly, while clustering by center is interesting, it will inherently bias against centers that accept referrals for complex patients.

Reply 2): Thanks for your valuable comments. We have added the assessing method of the model. In addition, we will add a random effect term in the regression models to control the bias raised by different clinical characteristics of patients in different research centers. Please refer to the detailed information as follow:

According to the results of univariate analysis, we preliminarily select the potential predictors for the multiple analysis. Then, multiple regression models are used to estimate the association between potential predictors and the outcomes of interest. For continuous dependent variables such as length of stay in ICU and hospital, multiple linear regression models are used. For categorical dependent variables such as the success of weaning, logistic regression or Cox regression models will be used. Given that patients in different centers may have different clinical characteristics, random effects term are added in models to control the related bias.

Based on the above models, we can identify the significant predictors and construct the predicted models. The predictors in models will be further refined based on the R^2, root mean square error (RMSE), Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC). In addition, half participants will be randomly selected

as trained samples and used to reconstruct the refined model with the same predictors. Another half participants will be used to test the accuracy of our model, which will be measured by sensitivity and specificity.

Changes in the text: Page 8, line 241-153.

3) The statistical considerations section is problematic. A retrospective descriptive cohort study should not use a sample size calculation. I'm not sure why the bronchospasm and pneumonia categorization suddenly appeared in this section. Why only these two variables? There is no need to include the equations for linear or logistic regression. These are standard, and need only be referenced. More important is the planned analysis of which variables will be included and why? P values? Clinical belief? Prior studies?

Reply 3): Thanks for your suggestion. We have removed the calculation of sample size. We have also removed the equations for linear and logistic regression. In addition, we have also listed the potential predictors of our study and explained of why such variables will be included.

Changes in the text: Page 8, line 228-232.2.5.

Potential Predictors

Based on the previous studies and our clinical experience, we selected the following potential predictors in the current study.

1)Respiratory (such as Bronchospasm, pneumonia);

2)Circulation(such as BNP, CVP, CI, urinary output, fluid balance)

Reference:

36.Lai YC, Ruan SY, Huang CT, Kuo PH, Yu CJ. Hemoglobin levels and weaning outcome of mechanical ventilation in difficult-to-wean patients: a retrospective cohort study. PLoS One. 2013 Aug 28;8(8): e73743. doi: 10.1371/journal.pone.0073743. PMID: 24015310; PMCID: PMC3756003.

37.Beuret P, Roux C, Auclair A, Nourdine K, Kaaki M, Carton MJ. Interest of an objective evaluation of cough during weaning from mechanical ventilation. Intensive Care Med. 2009 Jun;35(6):1090-3. doi: 10.1007/s00134-009-1404-9. Epub 2009 Jan 24. PMID: 19169666.

38.Liu L, Yin C, Zhi Y, Gao X, Xu L. [Preliminary establishment of weaning prediction model]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020 Feb;32(2):171-176. Chinese. doi: 10.3760/cma.j.cn121430-20191015-00032. PMID: 32275001.

Minor Issues:

1) The secondary outcomes list ICU and hospital mortality twice
   Reply 1): Thank you for your reminding. We have corrected.
   Changes in the text: Page 7, line 222-226.
2) Grammar needs to be reviewed.
   Reply 2):Thanks for your encouragement. This manuscript has been revised accordingly.
3) The plan to use simple, difficult and prolonged classification is interesting, but it

is unclear how it will be applied to this cohort.

Reply 3):Thank you for yourquestion. According to the reference, the patients were classified into one of three groups based on the difficulty and duration of the weaning process as follows: simple weaning, patients who proceed from initiation of weaningto successful extubation on the first attempt without difficulty; difficult weaning, patients whofail initial weaning and require up to three SBTs or as long as 7 days from the first SBT toachieve successful weaning; or prolonged weaning, patients who require more than three SBTsor >7 days of weaning process after the first SBT. From this reference, we think the weaning patients should be divided into three types at least. Each type has its suitable weaning strategy.

Changes in the text: Page 10, line356

4) The time period chosen includes COVID patients. This should be explicitly mentioned and a plan for their analysis included.

Reply 4: Thank you for your advice. COVID patientswere not included.

Changes in the text: See page 4, line 131.

Figures and tables:

Figure 1 is unnecessary and does not add to the document. Would remove. A flow diagram of patient fallout should be included in the actual study.

Reply: Thank you for your reminding. We have removed Figure 1.Because of the lack of data, we have not included a flow diagram of patient fallout in the actual study.Instead of adding a flow diagram, more detailedexclusion criteriafor patients has been described in patient screening section. (please refer to page 4, lines 136 to 140)