PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Fibroproliferative Changes on High-Resolution Computed Tomography in the Acute Respiratory Distress Syndrome Predict Mortality and Ventilator Dependency: A Prospective Observational Cohort Study
AUTHORS	Kazuya Ichikado, Hiroyuki Muranaka, Yasuhiro Gushima, Toru Kotani, Habashi M. Nader, Kiminori Fujimoto, Takeshi Johkoh, Norihiro Iwamoto, Kodai Kawamura, Junji Nagano, Kohichiro Fukuda, Naomi Hirata, Takeshi Yoshinaga, Hidenori Ichiyasu, Shinsuke Tsumura, Hirotsugu Kohrogi, Atsushi Kawaguchi, Masakazu Yoshioka, Tsutomu Sakuma and Moritaka Suga

VERSION 1 - REVIEW

REVIEWER	G. Umberto Meduri, M.D. Memphis VA Medical Center Professor of Medicine Division of Pulmonary, Critical Care, and Sleep Medicine University of Tennessee HSC I have no conflict of interest
REVIEW RETURNED	18/11/2011

GENERAL COMMENTS	This is well designed and conducted study. I have suggestions for changes related to the temporal progression of “fibroproliferation” and request the authors to provide more details about methylprednisolone treatment Specifics: Page 7. First sentence. • I refer the authors to a recent review in Chest that provides an updated view of fibro-proliferation as part of the tissue host defense response (HDR) - a tissue-protective reaction that consists of an integrated network of three simultaneously activated pathways [inflammation, coagulation, and tissue repair (fibro-proliferation is one component of tissue repair)], which account for the histologic and physiologic changes observed with progression (maladaptive response) or resolution (adaptive response) of ARDS and MODS. Systemic inflammation is the driver – prostrated elevation of pro-inflammatory cytokines parallels the elevation of procollagen in circulation and BAL. [Meduri GU, et al. S. Activation and Regulation of Systemic Inflammation in ARDS: Rationale For Prolonged Glucocorticoid Therapy. Chest 2009; 136: 1631-1643]. • Systemic inflammation is driven at cellular level by NF-Kb and regulated by the activated glucocorticoid receptor (GR). In open lung

	biopsies excess NF-Kb vs GR DNA binding is associated with worsen fibroproliferation. [Meduri GU, Muthiah P., Carratu P, ElTorky M, Chrousos G. Activation and regulation of systemic inflammation during acute respiratory distress syndrome. Interaction between nuclear factor-kB and glucocorticoid receptors and its effect on the transcription of inflammatory cytokines. NeuroImmunoModulation 2005; 12: 321-338. http://www.ncbi.nlm.nih.gov/] • The authors correctly state that fibroproliferation is an early event and conclude that an exaggerated initial inflammatory response [see discussion page 19] – leading to fibroproliferation – is a poor outcome indicator.. The two articles cited above provide the link between the two and may help frame pathophysiologically your presentation. Page 7. Third-fourth sentences. The statement is incorrect. The evolution of PaO2/FiO2 ratio correlates with progression vs resolution of ALI-ARDS. See above reference Page 7. Third-fourth sentences. “High-resolution computed tomographic (HRCT) findings correlate with the pathologic phases of diffuse alveolar damage” • References 12-14 refer to acute interstitial pneumonitis – This is not truly representative of early ARDS, since the disease process is much older by the time the patient presents to the ICU. Please ad some clarification. • Reference 15 (an excellent study) – relates to ARDS with CT obtained within 7 days of diagnosis. Page 8. Second sentence. You should insert here - a sentence characterizing ARDS as a systemic disease – with systemic inflammation as core pathogenetic process that affects the lungs as well as extra-pulmonary vital organs. Page 9. “On the response to treatment” - Under results = No data is presented Page 9. – “sequential CT scans were hard to be performed after high positive end-expiratory pressure ventilation was introduced …” - Clarify is the PEEP shown in table 1 is the one applied at the time of the above procedure? Page 11. – “Although the efficacy of steroids in ARDS patients has been controversial26 • Reference 28 Tang – a meta-analysis limited to prolonged steroid use – is in favor of steroid use. • Reference 27 Peter – a meta-analysis combining prolonged [similar to Tang] and one old trial with one day of massive steroid use – is inconclusive for mortality benefit. Change the sentence to – “While there is contracting reports for a survival benefit, all randomized trials have shown a significant reduction in duration of mechanical ventilation (Chest 2009; 136: 1631-1643) Page 11. “we examined the relationship between the efficacy of steroids and the extent of fibroproliferation on HRCT scans” - No data available are presented

	• Please provide information on dosage duration of treatment for both low and high dose. Include use (Yes/No) of surveillance surveillance. Since all patient received steroid treatment how do you plan to "examine relationship between the efficacy of steroids and the extent of fibroproliferation"?? It will be important to know if the HRCT score or one or more of the six parameter evaluated correlates with response. This might be a very important clinical application. Also define response to steroid treatment as mortality and ALSO other patient-ceneterd outcome such as duration of mechanical ventilation etc. See prior study below – comparing histology (late ARDS) to GC response (rapid vs delayed) Meduri GU, Chinn AJ. Fibroproliferation in late ARDS: pathophysiology, clinical and laboratory manifestations and response to corticosteroid rescue treatment. Chest 1994; 105: 127S-129S. Link to PubMed. • Page 14. Change "smaller SOFA" to "lower SOFA" Discussion Page 20 – Again (see first recommended reference) – Dysregulated systemic inflammation – characterized by persistent elevation in circulating markers of inflammation- coagulation-fibro proliferation) is the core pathogenetic process leading to morbidity and mortality in ARDS. VAP results from exaggerated inflammation (growth factors for bacteria that cause VAP) and VAP rate is decreased with GC-induced downregulation of systemic inflammation (Meduri GU. Clinical review: the bi-directional effect of inflammation on bacterial growth. Clinical implications for patients with ARDS. Critical Care 2002; 6: 24-29. (with editorial). Link to PubMed. Addition paper of potential interest.. Meduri GU, Eltorky M, Winer-Muram HT. Fibroproliferative phase of late ARDS. Seminars in Respiratory Infections 1995; 10: 152-173. Link to PubMed. In conclusion – this is very important study – I believe that you place your findings in the present pathophysiological understanding of ARDS and provide the necessary details to understand how the HRCT finding can be used to predict steroid response your paper will be well received by the clinical community and will be frequently quoted in the literature You can reach me at gmeduri@uthsc.edu if you need additional clarifications

REVIEWER	Prof. Dr. Marcelo Gama de Abreu, Vice-Director Head of Research, Department of Anesthesiology and Intensive Care, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany. No conflicts of interest.
REVIEW RETURNED	10/12/2011

THE STUDY	The manuscript needs improvement in grammar, spelling and style.
GENERAL COMMENTS	General comments Ichikado and colleagues assessed the extension of lung fibroproliferative changes in patients with ARDS by high resolution computed tomography (HRCT), and determined its prognostic value in terms of mortality and a number of relevant secondary outcomes. Authors found that pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality with an increased susceptibility to multiple organ failure, including ventilator dependency and its associated outcomes. The issue addressed has high clinical relevance and the work seems to have been carefully performed, building on previous publications of the same group. Also the different analyses of inference are elegant and I congratulate the authors for their job. The manuscript would benefit from a revision of spelling and grammar, but it is nicely written. In my view, the only weakness is the analysis of use of steroids and the HRCT. Authors should better explain the rationale for that, or skip this analysis. It was a pleasure for me to review this manuscript. Specific comments Abstract Page 4, lines 48-49: please try “statistically significant decreases in …”. Introduction Page 8, line 14: “pathologically divided” – please reword. Material and Methods Was this study registered in a clinical trials registry? Page 10, lines 48-51: Averages of assessments is reasonable, but please let us know who were the investigators and whether they have been trained for this task. Page 12, line 22: on the Management of … Page 12, lines 24-46: I got very surprised with this paragraph. I know this is a non-randomized controlled trial, but the new task, namely assessing the effects of steroids has not been mentioned previously. Furthermore, why is the rationale for addressing steroids if the CT was performed “at diagnosis” of ARDS? Page 13, line 43: Why only “without assistance”? What do you mean? Results I am just curious: do you have PaCO2 or data on deadspace values of those patients? If this is the case, a correlation analysis of the HRCT with deadspace would be interesting. Page 15, lines 24-25: What are “therapeutic variables”? Please reword. Figure 1: “Died at day 180” is misleading. Please correct. Discussion Page 18, line 53 to Page 19, line 6: In fact, findings of early and late phase of ARDS frequently overlap. Please introduce that concept here. Please spend some words on the issue of steroids and HRCT, if you can explain the rationale for that analysis. Also, please include in the limitations some words on the cutoff values and extrapolation to other patients.

VERSION 1 – AUTHOR RESPONSE

From Reviewer (Dr. Meduri):

1. According to your suggested papers including an updated review of fibro-proliferation, we also believe that they may pathophysiologically support our presentation. We added one of the papers to reference 29.

2. (page 7, third-fourth sentences in Introduction) You asked us to correct the sentence. According to your comment, we added a sentence as follows: Although pathologic staging may be conceptually useful, commonly used clinical indicators such as PaO2/FiO2 ratio correlate with progression or resolution of ARDS but necessarily reflect the extent of fibroproliferation.

3. (page 7, third-fourth sentences in Introduction) You ask us to clarify the application of the results of HRCT findings correlated with pathology in patients with acute interstitial pneumonia (AIP) to early ARDS. AIP is pathologically characterized by organizing diffuse alveolar damage (DAD) which is identical to the alveolar damage found in ARDS and is considered an idiopathic DAD/ARDS. In our previous studies of AIP (reference 11,13), we have experienced cases of AIP who histologically showed not only the organizing /proliferative phase but also the exudative phase of DAD. Therefore, we believe that HRCT findings correlate with the pathologic phases of diffuse alveolar damage in patients with ARDS as well as in those with AIP.

4. (page 8, second sentence in Introduction) Per your comment, we added the sentence as follows: In this prospective study, because of ARDS as a systemic disease with systemic inflammation as core pathogenetic process that affects the lung as well as extra-pulmonary vital organs, we evaluated not only what was found in the retrospective study15 but also the relationship between early fibroproliferation and the progression to multiple organ failure.

5. (page 8, third sentence, line 22 in Introduction) According to your comment, we have changed “on the response to treatment” to “on the mortality”.

6. (page 9, lines 38-43) You asked us to clarify when the PEEP shown in Table 1 was applied. We started the high positive end-expiratory pressure ventilation shown in Table 1 in our intensive care unit after we performed CT scans.

7. (page 11, lines 25-30 in Methods) You asked us to change the sentence as follows: While there is contracting reports for a survival benefit, all randomized trials have shown a significant reduction in duration of mechanical ventilation. We added your paper (Chest 2009;136:1631-1643) to Reference 29.

8. (page 11, lines 30-35 in Methods) You asked us to provide information on dosage, duration of corticosteroid treatment. We added a following sentence: Initial administration of methylprednisolone with a moderate dose (2 mg/kg/day) (n = 71) or high-dose (1000 mg/day for three days followed by a moderate dose) (n = 14) was introduced and was gradually tapered over one month according to the previous study(ref.30)

9. (page 14, line 19 in Results) According to your comment, we changed “smaller SOFA” to “lower SOFA”.

10. (page 20, lines 27-32 in Discussion) According to your suggestion, we added a following sentence: Furthermore, sustained and intense inflammatory responses in unresolving ARDS increase the bi-directional effects on bacterial growth40. In addition that, we referenced your paper as #40.

From Reviewer (Dr. Marcelo Gama):

1. (page 4, lines 48-49 in Abstract) Considering the reviewer comment, we changed “significantly decreased number of organ failure free days---” to “statistically significant decreases in organ failure free days as well as ventilator-free days“.

2. (page 8, line 14 in Introduction)
According to your comment, we changed “pathologically divided” to “pathologically classified”.

3. Materials and Methods
You asked us whether this study was registered in a clinical trials registry. We did not register this study.

4. (page 10, lines 48-51 in Materials and Methods)
You asked us to let you know who were investigators and whether they have been trained for this task. We added the following phrase: by two independent observers (K.Fujimoto. and T.J.) who were chest radiologists with 23 and 20 years of experience, respectively, and were unaware of patient condition.
4. (page 12, line 22 in Materials and Methods)
According to your comment, we corrected the sentence as follows: Antibiotic therapy was performed by these guidelines, which were referenced to the American Thoracic Society/Infectious Diseases Society of America Consensus Guidelines on the management of community-acquired pneumonia in immunocompetent adults.
5. (page 12, lines 24-26 in Materials and Methods)
You asked us to clarify why is the rationale for addressing steroids if the CT was performed “at diagnosis” of ARDS. We added following sentences for explanation : According to our previous study(ref. 15), early fibroproliferation on HRCT scans was observed in 64 % of 44 patients with ARDS. Therefore, we started corticosteroid therapy after performing HRCT scans at the diagnosis of ARDS.
6. (page 13, line 43 in Outcome measurements)
You asked us to explain “while alive without assistance” in the definition of survivors. We appreciate your suggestion and deleted “without assistance”.
7. Results
We appreciate your comment. We did not have data on deadspace values of our patients and would like to study a correlation analysis of the HRCT with deadspace values.
8. (page 15, lines 24-25 in Baseline clinical characteristics)
You asked us to reword “therapeutic variables”. We changed ““therapeutic variables” to “ventilatory and medicational conditions”.
9. (Figure 1) You asked us to correct “Died at day180” in Figure 1. We corrected “Died until day 180” and “Died until day 60”.
10. Discussion
(page 18, line 53 to page 19, line 6) According to your comment, we added the following sentence : We also confirmed that HRCT findings of early and late phase of ARDS frequently overlapped.
11. You and the other reviewer (Dr. Meduri) asked us to explain the rationale for the issue of steroid and HRCT findings. We discussed about this matter as follows: Persistent dysregulated systemic inflammation leading to maladaptive lung repair results in pulmonary fibroproliferation and progression of extrapulmonary organ dysfunction (ref. 29). Prolonged corticosteroid therapy attenuates systemic inflammation and reduced duration of mechanical ventilation (ref. 29). In our study, the group of patients who had less fibroproliferative changes on HRCT scans (HRCT score, < 210) showed lower mortality and more ventilator-free days than those who had more extensive areas of fibroproliferation (HRCT score, ≥ 210). This may suggest a relationship between the pathologic phases of ARDS and responsiveness to treatment. More extensive and rapidly progressive pulmonary fibroproliferation resulting from intense exaggerated systemic inflammation at presentation occurs, less effective even prolonged corticosteroid therapy may be.
12. You asked us to mention the cutoff values and extrapolation to other patients in the limitations of our study. We added the following paragraph in the limitations of our study: Fourth, when using our cutoff values of HRCT scores, there were approximately 25 % of our patients who did not fit for prediction of poor prognosis or ventilator dependency. Recently, multiple organ failure in ARDS patients is considered to be either as the predisposing condition or as a consequence of ARDS (ref. 42). If ARDS occurs as one of multiple organ failure, even though pulmonary fibroproliferation was mild, extrapulmonary dysfunction could be the determinant of the outcome.

Thank you again for your decision for our manuscript. We are sorry to be late for our revised manuscript. We look forward to your further response.

Sincerely yours,

Kazuya Ichikado, M.D., PhD
Division of Respiratory Medicine
Saiseikai Kumamoto Hospital

VERSION 2 – REVIEW

REVIEWER	G. Umberto Meduri, M.D. Memphis VA Medical Center Professor of Medicine Division of Pulmonary, Critical Care, and Sleep Medicine University of Tennessee HSC I have no conflict of interest
REVIEW RETURNED	03/01/2012

GENERAL COMMENTS	Insert in page 7 “Fibroproliferation is part of the tissue host defense response (HDR) - a tissue-protective reaction that consists of an integrated network of three simultaneously activated pathways [inflammation, coagulation, and tissue repair (fibroproliferation is one component of tissue repair)], which account for the histologic and physiologic changes observed with progression (maladaptive response) or resolution (adaptive response) of ARDS and MODS 29. Page 8 Change "Although pathologic staging may be conceptually useful, commonly used clinical indicators such as PaO2/FiO2 ratio correlate with progression or resolution of ARDS but necessarily reflect the extent of fibroproliferation. " "Although pathologic staging may be conceptually useful, improvement vs. worsening in physiological parameters (i.e., PaO2/FiO2 ratio, etc.) over time correlates with adaptive vs. maladaptive lung repair and outcome." Page 20 - Change "Furthermore, sustained and intense inflammatory responses in unresolving ARDS increase the bi-directional effects on bacterial growth40" to Furthermore, sustained and intense inflammatory responses in unresolving ARDS increase intracellular and extra-cellular growth of nosocomial pathogens and increase the risk for nosocomial infections 40

REVIEWER	Prof. Dr. Marcelo Gama de Abreu, Department of Anesthesiology and Intensive Care, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany. I have no conflict of interest related to this manuscript.
REVIEW RETURNED	15/01/2012

THE STUDY	With the new sentences, more grammar errors were introduced.
GENERAL COMMENTS	I thank the authors for addressing the issues I raised in my previous comments, and changing the text accordingly.

	I must apologize for not asking for the following change before: both in the Abstract and the Materials and Methods section, you refer to "primary outcomes", namely mortality at 60 and 180 days. I suggest you using only one primary outcome. Page 17, lines 14-25: Please rephrase "In this prospective study, because of ARDS as a systemic disease with systemic inflammation as core pathogenetic process that affects the lung as well as extra-pulmonary vital organs, we evaluated not only what was found in the retrospective study but also the relationship between early fibroproliferation and the progression to multiple organ failure;". The sentence is clumsy and difficult to read. Page 20, lines 37-38: "While there is contracting reports ...". You probably mean contradicting reports. Page 31, lines 29-36: "More extensive and rapidly progressive pulmonary fibroproliferation resulting from intense exaggerated systemic inflammation at presentation occurs, less effective even prolonged corticosteroid therapy may be." Please rephrase.

VERSION 2 – AUTHOR RESPONSE

From Reviewer (Dr. Gianfranco Meduri):
1. (page 7, lines 9-14 in Introduction) You ask us to insert the following sentences in Introduction. According to your suggestion, we inserted the sentences: Fibroproliferation is part of the tissue host defense response – a tissue-protective reaction that consists of an integrated network of three simultaneously activated pathways [inflammation, coagulation, and tissue repair (finbroproliferation is one component of tissue repair)], which account for the histologic and physiologic changes observed with progression (maladaptive response) or resolution (adaptive response) of ARDS and multiple organ failure syndrome5.
2. (page 8, lines 14-16 in Introduction) You asked us to change the sentences. According to your comment, we changed the sentence as follows: Although pathologic staging may be conceptually useful, improvement vs. worsening in physiological parameters (i.e., PaO2/FiO2 ratio, etc) over time correlates with adaptive vs. maladaptive lung repair and outcome.
3. (page 21, lines 11-14 in Discussion) You ask us to change the sentences. According to your suggestion, we changed the sentence as follows: Furthermore, sustained and intense inflammatory responses in unresolving ARDS increase intracellular and extra-cellular growth of nosocomial pathogens and increase the risk for nosocomial infections 40.
From Reviewer (Dr. Marcelo Gama de Abreu):
1. You asked us to select either mortality at 60 days or at 180 days as only one primary outcome. According to your comment, we decided mortality at 60 days as the primary outcome.
(page 4, line 13 in Abstract, we deleted 180-day mortality.): The primary outcome was 60-day mortality.
(page 5, line 4-6 in Abstract, we changed " prediction of 180 day survival with 71 % sensitivity and 76 % specificity" to the following.) An HRCT score < 210 enabled prediction of 60 day survival with 71 % sensitivity and 72 % specificity.
(page 13, lines 12-13 in Outcome measurements): The primary outcome was mortality 60 days after ARDS diagnosis. Patients discharged from the hospital while alive for 60 days were defined as survivors. Their prognoses were eventually followed until 180 days.
2. (page 8, lines 10-14 in Introduction) According to your comment, we changed the sentences as follows: Because ARDS is a systemic disease with systemic inflammation, core pathogenetic process affects the lung as well as extra-pulmonary vital organs. In this prospective study, we evaluated not only what was found in the retrospective study16 but also the relationship between early

fibroproliferation and the progression to multiple organ failure
3. (page 11, lines 19-20 in Treatment Protocol) According to your comment, we corrected the sentences: While there is contradicting reports for a survival benefit, all randomized trials have shown a significant reduction in duration of mechanical ventilation27-30.
4. (page 22, lines 9-12 in Discussion)
You asked us to rephrase the sentences. We changed the sentences as follows: When more extensive and rapidly progressive pulmonary fibroproliferation resulting from intense exaggerated systemic inflammation at presentation occurs, even prolonged corticosteroid therapy may not be effective.

Thank you very much again for your decision for our manuscript. We look forward to your further response.

Sincerely,

Kazuya Ichikado, M.D., PhD
Division of Respiratory Medicine
Saiseikai Kumamoto Hospital, Japan

REVIEWER	Prof. Dr. Marcelo Gama de Abreu, Department of Anesthesiology and Intensive Care, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany. I have no conflict of interest related to this manuscript.
REVIEW RETURNED	04/02/2012

GENERAL COMMENTS	Thank you for addressing all my concerns and congratulations for the nice work. I have no further suggestions.