**Supplementary data in this cohort**

Title: Clinical characteristics and outcome of COVID-19-Associated pulmonary Aspergillosis patients (CAPA): a systematic review and meta-analysis with 29 cohort studies

Authors: Wensen Chen, Cheng Yin, Ming Zhong, Bijie Hu, Xiaodong Gao, Kai Zhang, Yun Liu, Guihua Zhuang

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| **Supplementary 1 Characteristics of 29 cohort studies in this meta-analysis** | | | | | | | | | | | | | |
| **Author** | **Publication Year** | **Participants** | **Study Design** | **Study period** | **Location of Study** | **Characteristics of the patients** | **Patients investigate for CAPA** | **CAPA** | **CAPA Incidence** | **Mortality** | **CFR** | **Quality assessment by NOS** | **Follow up** |
| **Alanio A, et al.** | 2020 | 27 successive mechanically ventilated  patients with COVID-19 | Prospective cohort study |  | France |  | 27 | 9 | 9/27 | 4/27 | 4/9 | 3 |  |
| **Van Biesen S, et al.** | 2020 | 42 critically ill COVID-19 patients | Retrospective cohort study | 3-week time frame in April 2020 | Netherlands | MV | 42 | 9 | 9/42 | 2/42 | 2/9 | 5 | 30-day from ICU admission |
| **Buehler PK,et al.** | 2020 | 45 critically ill COVID-19 patients | Prospective cohort study | April to June, 2020 | Switzerland | ARDS | 45 | 5 | 5/45 | 3/45 | 3/5 | 5 | ventilator-free on day 28 |
| **Charalampous T, et al.** | 2020 | 274 intubated patients across seven COVID-19 intensive care units | Prospective cohort study | March 20 to June 24, 2020 | UK | MV; | 225 | 9 | 9/225 | NR | NR | 5 | NR |
| **Dupont D, et al.** | 2020 | 153 consecutive adult intensive care unit (ICU) patients | Retrospective cohort study |  | France | ARDS | 106 | 19 | 19/106 | 7/106 | 7/19 | 5 | 42-day from ICU admission |
| **Helleberg M, et al** | 2020 | 8 COVID-19 patients with ECMO | Retrospective cohort study | March 15 to November 4, 2020 | Denmark | ECMO | 8 | 2 | 2/8 | 2/8 | 2/2 | 4 |  |
| **Bartoletti M, et al.** | 2020 | 108 COVID-19 patients | Multi-center prospective cohort study | February 22 to April 20, 2020 | Italy | MV, ARDS | 108 | 30 | 30/108 | 13/108 | 13/30 | 7 | median follow-up :31 (20- 43) days from ICU admission |
| **Borman AM, et al.** | 2021 | 719 critically ill UK patients with COVID-19 | Retrospective cohort study | March 11 to July 14, 2020 | UK |  | 61 | 13 | 13/61 | NR | NR | 3 |  |
| **Chauvet P, et al.** | 2020 | 46 COVID-19 patients with acute respiratory distress syndrome | Retrospective cohort study | March 24 to May 25, 2020 | France | ARDS | 46 | 6 | 6/46 | 4/46 | 4/6 | 5 | 60-day from ICU admission |
| **Delliere S, et al.** | 2021 | 366 successive COVID-19 patients, hospitalized in four ICUs | Multi-centric retrospective cohort | March 15 to May 1, 2020 | France |  | 108 | 21 | 21/108 | 15/108 | 15/21 | 6 |  |
| **Fekkar A, et al.** | 2020 | 260 patients were admitted to the ICU for severe COVID-19 | Retrospective cohort study | March 6 to April 24, 2020 | France |  | 145 | 7 | 7/145 | 4/145 | 4/7 | 7 | 30-day from ICU admission |
| **Gangneux JP,et al.** | 2020 | 45 COVID-19 patients | Prospective cohort study |  | France | MV, ARDS | 45 | 7 | 7/45 | 2/45 | 2/7 | 6 | ventilator-free， 28-day |
| **Gouzien L, et al.** | 2021 | 53 critical ill COVID-19 patients | Retrospective cohort study | March 1 to April 30, 2020 | France | MV | 53 | 1 | 1/53 | NR | NR | 4 | 90-day from ICU admission |
| **Van Grootveld R, et al.** | 2020 | 63 COVID-19 patients admitted to the ICU | Prospective cohort study | April 1 to May 11, 2020 | Netherlands | MV | 63 | 11 | 11/63 | 7/63 | 7/11 | 5 | 45-day from ICU admission |
| **Koehler P,et al.** | 2020 | 19 consecutive critically ill patients with moderate to severe ARDS | Retrospective cohort study | March to April, 2020 | Germany | ARDS | 19 | 5 | 5/19 | 3/19 | 3/5 | 3 |  |
| **Lahmer T, et al.** | 2020 | 32 adults Patients (≥18 years) with severe COVID-19 | Prospective cohort study | March to April 2020 | Germany | MV, ARF | 32 | 11 | 11/32 | 4/32 | 4/11 | 7 | 28-day from ICU admission |
| **Lamoth F,et al.** | 2020 | 118 patients admitted to ICUs with confirmed COVID-19 | Prospective cohort study | March 6 to May 11, 2020 | Switzerland | MV | 80 | 3 | 3/80 | 1/80 | 1/3 | 3 |  |
| **Maes M, et al.** | 2020 | 81 COVID-19 and 144 non-COVID-19 patients | Retrospective cohort study | March 15 to August 30, 2020 | UK | MV | 23 | 3 | 3/23 | NR | NR | 6 | 37-day from ICU admission |
| **Meijer EF,et al.** | 2020 | 573 COVID-19 patients and 66 needed intubation | Prospective cohort study | March-May 2020 and mid-September through mid-December 2020 | Netherlands | MV | 66 | 13 | 13/66 | 6/66 | 6/13 | 4 |  |
| **Mitaka H,et al.** | 2020 | 7 patients with COVID-19 underwent mechanically ventilated in the ICU | Retrospective cohort study | March 21 to April 22, 2020 | USA |  | 7 | 4 | 4/7 | 4/7 | 4/4 | 3 |  |
| **Nasir N, et al.** | 2020 | 147 patients with confirmed COVID-19 and 23 (15.6%) patients requiring ICU  admission | Retrospective cohort study | Feruary to April, 2020 | Pakistan | ARDS | 23 | 5 | 5/23 | 3/23 | 3/5 | 6 | 35-day from ICU admission |
| **Nebreda-Mayoral T, et al.** | 2020 | 113 COVID-19 patients and 50 patients in ICU | Retrospective cohort study | March1to May31,2020 | Spain | MV | 50 | 3 | 3/50 | 1/50 | 1/3 | 4 |  |
| **RazaziK, et al.** | 2020 | 172 patients,90 COVID-19-related acute respiratory distress syndrome and 82 non-SARS-CoV-2 viral ARDS | Retrospective cohort study | October 1 2009 to April 29, 2020 | France | MV;ARDS | 90 | 7 | 7/90 | NR | NR | 7 | Minimal follow-up period of 28-day from ICU admission |
| **Roman-Montes CM,et al.** | 2020 | 144 COVID-19 critical ill patients | Retrospective cohort study | April 13 to June 1, 2020 | Mexico | MV | 144 | 14 | 14/144 | 8/144 | 8/14 | 6 | 28-day from ICU admission |
| **Rutsaert L, et al.** | 2020 | 34 critically ill COVID-19 patients | Retrospective cohort study | March 12 to April 25, 2020 | Belgium | MV | 20 | 7 | 7/20 | 4/20 | 4/7 | 3 |  |
| **Segrelles-Calvo G,et al.** | 2020 | 215 adult patients respectively admitted to ICU with COVID-19 | Prospective cohort study | February 1 to April 30, 2020 | Spain |  | 215 | 7 | 7/215 | 5/215 | 5/7 | 5 |  |
| **van Arkel ALE, et al.** | 2020 | 31 patients admitted to ICUs with confirmed COVID-19 | Retrospective cohort study |  | Netherlands | MV | 31 | 6 | 6/31 | 4/21 | 4/6 | 4 | 42-day from ICU admission |
| **Wang J,et al** | 2020 | 104 patients with COVID-19 | Retrospective cohort study | January to March , 2020 | China |  | 78 | 8 | 8/78 | NR | NR | 4 |  |
| **White PL, et al.** | 2020 | 135 COVID-19 patients | National, multi-centre, prospective cohort |  | UK | MV | 135 | 19 | 19/135 | 11/135 | 11/19 | 6 | 30-day from ICU admission |

Abbreviation: CAPA, COVID-19-associated pulmonary aspergillosis; CFR, Case fatality rate; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure;

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| **Supplementary 2 Quality of all included studies using the Newcastle–Ottawa Scale (NOS)** | | | | | | | | | | |
| **Study** | **Publication Year** | **NOS Score** | ***SELECTION*** | | | | **COMPARABILITY** | ***OUTCOME*** | | |
| **Representativeness of the Exposed Cohort** | **Selection of the Non-Exposed Cohort** | **Ascertainment of Exposure** | **Outcome of Interest Was Not Present at Start of Study** | **Comparability of Cohorts** | **Assessment of Outcome** | **Follow-Up Long Enough** | **Adequacy of Follow Up** |
| **Charalampous T, et al.** | 2020 | ☆☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ | ☆ |
| **Borman AM, et al.** | 2021 | ☆☆☆ |  | ☆ |  | ☆ |  | ☆ |  |  |
| **Rutsaert L, et al.** | 2020 | ☆☆☆ |  | ☆ |  | ☆ |  | ☆ |  |  |
| **Koehler P,et al.** | 2020 | ☆☆☆ |  | ☆ |  | ☆ |  | ☆ |  |  |
| **Nasir N, et al.** | 2020 | ☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ |  | ☆ | ☆ | ☆ |
| **Van Biesen S, et al.** | 2020 | ☆☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ | ☆ |
| **Bartoletti M, et al.** | 2020 | ☆☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ |
| **Lamoth F,et al.** | 2020 | ☆☆☆ |  | ☆ |  | ☆ |  | ☆ |  |  |
| **Nebreda-Mayoral T, et al.** | 2020 | ☆☆☆☆ |  | ☆ |  | ☆ | ☆ | ☆ |  |  |
| **Lahmer T, et al.** | 2020 | ☆☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ |
| **RazaziK, et al.** | 2020 | ☆☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ |
| **Chauvet P, et al.** | 2020 | ☆☆☆☆ ☆ |  | ☆ |  | ☆ |  | ☆ | ☆ | ☆ |
| **Fekkar A, et al.** | 2020 | ☆☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ |
| **Mitaka H,et al.** | 2020 | ☆☆☆ |  | ☆ |  | ☆ |  | ☆ |  |  |
| **Dupont D, et al.** | 2020 | ☆☆☆☆ ☆ |  | ☆ |  | ☆ |  | ☆ | ☆ | ☆ |
| **Alanio A, et al.** | 2020 | ☆☆☆ |  | ☆ |  | ☆ |  | ☆ |  |  |
| **Segrelles-Calvo G,et al.** | 2020 | ☆☆☆☆ ☆ |  | ☆ | ☆ | ☆ |  | ☆ | ☆ |  |
| **Helleberg M, et al** | 2020 | ☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ |  |
| **van Arkel ALE,et al.** | 2020 | ☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ |  |
| **Meijer EF,et al.** | 2020 | ☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ |  |
| **Gouzien L, et al.** | 2021 | ☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ |  |
| **Maes M, et al.** | 2020 | ☆☆☆☆☆☆ |  | ☆ |  | ☆ | ☆ | ☆ | ☆ | ☆ |
| **Delliere S, et al.** | 2021 | ☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ | ☆ | ☆ | ☆ |  |
| **van Grootveld R, et al.** | 2020 | ☆☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ | ☆ |
| **White PL, et al.** | 2020 | ☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ |  | ☆ | ☆ | ☆ |
| **Roman-Montes CM,et al.** | 2020 | ☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ |  | ☆ | ☆ | ☆ |
| **Gangneux JP,et al.** | 2020 | ☆☆☆☆☆☆ |  | ☆ | ☆ | ☆ |  | ☆ | ☆ | ☆ |
| **Buehler PK,et al.** | 2020 | ☆☆☆☆☆ |  | ☆ |  | ☆ |  | ☆ | ☆ | ☆ |
| **Wang J,et al** | 2020 | ☆☆☆☆ |  | ☆ |  | ☆ | ☆ | ☆ |  |  |

Abbreviation: Newcastle–Ottawa Scale, NOS



**Supplementary 3 Figure A Publication bias with Egger’s test for incidence of CAPA among 29 cohort studies (t=8.95, P<0.001)**



**Supplementary 3 Figure B Publication bias with Egger’s test for mortality of CAPA among 29 cohort studies (t=8.25, P<0.001)**



**Supplementary 3 Figure C Publication bias with Egger’s test for CFR of CAPA**

**among 29 cohort studies (t=-1.59, p=0.129)**



**Supplementary 3 Figure D Publication bias with Egger’s test for mortality of CAPA compared with Non-CAPA (t=-1.59, p=0.129)**

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| Supplementary 4 Definition of CAPA in all included cohort studies | | | | |
| **Author** | **Publication Year** | **Clinical** | **Radiological** | **Microbiological** |
| **Charalampous T, et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **RazaziK, et al.** | 2020 | IAPA case definition, and modified AspICU definition | | |
| **Maes M, et al.** | 2020 | IAPA modified to include diagnosis by PCR | | |
| **van Grootveld R, et al.** | 2020 | 2020 ECMM/ISHAM consensus criteria | | |
| **White PL, et al.** | 2020 | PCR confirmed COVID-19 infection and one of: Refractory fever despite at least 3 days antibiotics Recrudescent fever of at least 48 hours despite antibiotics Dyspnoea Haemoptysis Pleural rub or chest pain Worsening respiratory function despite antibioticsand ventilatory support | New infiltrates on chest x-ray or chest CT when compared to admission,including progression of signs attributed to viral infection. Radiological signs typical of invasive pulmonary aspergillosis (nodules, halos, cavities, wedge-shaped and segmental or lobar consolidation) or evidence of sinusitis should be associated with heightened suspicion of fungal disease | **Proven:** Histology/Microscopy demonstrating dichotomous septatehyphae in tissue Positive culture from tissue. **Putative:** Non-specific radiology: Two or more positives across different test types, or multiple positives within one test type, from the following: Positive culture from NBL/BAL Positive GM-EIA in NBL/BAL (I≥1·0)Positive GM-EIA in serum (I≥0·5)Positive Aspergillus PCR in BAL or blood Positive 1-3-β-D-Glucan in serum/plasma  **Radiology typical of IA:** One positive mycological tests as listed above, unless the typical radiological signs can be attributed to a different underlying infection (e.g. lung cancer or alternative infection). In this scenario multiple positive results would be required to attain a diagnosis of putative IPA. Please note: Given the a etiological diversity associated with sinusitis, multiple positive tests from the list above are required to attain a diagnosis of putative IPA |
| **Roman-Montes CM,et al.** | 2020 | the modified AspICU Algorithm | | |
| **Gangneux JP,et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **Buehler PK,et al.** | 2020 | IDSA Practice Guidelines for the Diagnosis and Management of Aspergillosis (2016) | | |
| **Wang J,et al** | 2020 | EORTC/MSGERC | | |
| **Borman AM, et al.** | 2021 | the modified AspICU Algorithm | | |
| **Rutsaert L, et al.** | 2020 | AspICU algorithm, the EORTC criteria | | |
| **Koehler P,et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **Nasir N, et al.** | 2020 | clinical signs and symptoms ,lung imaging, respiratory specimen culture (bronchoalveolar lavage (BAL), tracheal aspirate or sputum) positive for Aspergillus spp. or a positive serum or lower respiratory samples galactomannan index of more than 0.5 and 1.0 respectively in patients who were either not improving from COVID-19 or who worsened after transient improvement of symptoms from COVID-19 | | |
| **Van Biesen S, et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **Bartoletti M, et al.** | 2020 | IAPA case definition | | |
| **Lamoth F,et al.** | 2020 | IAPA case definition | | |
| **Nebreda-Mayoral T, et al.** | 2020 | Not clearly described | | |
| **Lahmer T, et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **Chauvet P, et al.** | 2020 | AspICU criteria, EORTC-MSG criteria | | |
| **Fekkar A, et al.** | 2020 | Not clearly described | | |
| **Mitaka H,et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **Dupont D, et al.** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **Alanio A, et al.** | 2020 | EORTC-MSG criteria (if immunocompromised) or the IAPA criteria combined with serum β-D-glucan and quantitative real-time PCR (qPCR) | | |
| **Segrelles-Calvo G,et al.** | 2020 | EORTC/MSG criteria | | |
| **Helleberg M, et al** | 2020 | the modified AspICU criteria in patients with SARS-CoV-2 infection | | |
| **van Arkel ALE,et al.** | 2020 | IAPA case definition | | |
| **Meijer EF,et al.** | 2020 | ECMM/ISHAM consensus criteria | | |
| **Gouzien L, et al.** | 2021 | AspICU algorithm, the EORTC criteria,the expert consensus case criteria for IAPA, and Alanio’s definition | | |
| **Delliere S, et al.** | 2021 | EORTC/MSGERC consensus criteria in immunocompromised patients and according to the consensus case definition proposal for influenza-/COVID-19-associated pulmonary aspergillosis(CAPA) in ICU patients | | |
| **Abbreviation : CAPA, COVID-19-associated pulmonary aspergillosis; EORTC, European Organization for Research and Treatment of Cancer; MSGERC,the Mycoses Study Group Education and Research Consortium; IAPA: influenza-associated pulmonary aspergillosis** | | | | |

**Supplementary 5 Checklist of this study**

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| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 5 |

Page 1 of 2

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| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5 |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 5 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 6 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6,7,8 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6,7,8 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 6,7,8 |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 8,9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 9,10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9,10 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 11 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097