

## Peer Review File

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### Reviewer A

**Comment 1:** First, the title is very unclear, which should indicate the research work done by the authors but it looks like a review.

**Reply 1:** We thank the reviewer for this comment, and we agree with the fact that the title should emphasize more the type of research done. We thus added the main goal and the design of the study in the title of the revised version of the manuscript as follows below. The modification of the title also take into account the comment N°4 that suggest to change the term “retrospective study” into “case series study”.

**Changes in the text (title):** Diagnosis and prognosis of Acute Respiratory Distress Syndrome related to diffuse Pneumonic-type Adenocarcinoma: a single-center case series study

**Comment 2:** Second, the abstract is inadequate. In the background, the authors only indicated the knowledge gap but did not indicate the clinical relevance of the research topic. In the patients and methods part, please describe the inclusion of subjects, assessments of clinical characteristics and outcomes, and main statistical methods such as the logistic regression. The conclusion sentence is very crude, please provide more detailed comments on how to better recognize of the disease key features and make a timely diagnostic confirmation of P-ADC.

**Reply 2:** We thank the reviewer for these comments. We totally agree that the clinical relevance of the “absence of diagnosis of the cause of ARDS (or acute respiratory failure in general)” was lacking. We thus added in the revised version of the abstract the notion that the absence of diagnosis is demonstrated as an independent predictor of mortality in cancers patients. We also modified the methods in order to incorporate the inclusion criteria, outcomes and main statistical methods. We also agree with the fact that our conclusion was a bit “crude” and maybe excessively conclusive regarding mortality outcome. We thus summarize may diagnostic findings in the conclusion and moderate the association between delayed diagnosis and mortality. Thus the abstract has been substantially modified in it revised version in comparison with the initial version as follows below.

**Changes in the text (abstract):**

Background: The absence of diagnosis of acute respiratory distress syndrome (ARDS) concerns 20% of cancer patients and is associated with poorer outcomes. Diffuse peumonic-type adenocarcinoma (P-ADC) is part of these difficult-to-diagnose ARDS,

but only limited data are available regarding critically ill patients with diffuse P-ADC. We sought to describe the diagnosis process and the prognosis of P-ADC related ARDS patients admitted to the intensive care unit (ICU).

**Patients and Methods:** Single-center observational case series study. All consecutive patients admitted to the ICU over a two-decade period presenting with 1) histologically or cytologically proven adenocarcinoma of the lung and 2) ARDS according to Berlin definition we included. Clinical, biological, radiological and cytological features of P-ADC were collected to identify diagnostic clues. Multivariate logistic regression analyses were performed to assess factors associated with ICU and hospital mortality. **Results:** Among the 24 patients included (70 [61–75] years-old, 17 (71%) males), the cancer diagnosis was performed during the ICU stay in 19 (79%), and 17 (71%) required mechanical ventilation. The time between the first symptoms and the diagnosis of P-ADC was 210 (92–246) days. A non-resolving pneumonia after 2 (2–3) antibiotics lines observed in 23 (96%) patients with a 34 (19–75) mg/L plasma C-reactive protein level at ICU admission. Progressive dyspnea, bronchorrhea, salty expectoration, fissural bulging and compressed bronchi and vessels were present in 100%, 83%, 69%, 57% and 43% of cases. Cytological examination of sputum or broncho-alveolar lavage provided a 75% diagnostic yield. The ICU and hospital mortality rates were 25% and 63%, respectively. The time (in days) between first symptoms and diagnosis (Odds ratio [OR] 1.02, 95% confidence interval [95%CI] 1.00–1.03,  $p=0.046$ ) and the Simplified Acute Physiology Score 2 (OR 1.16, 95%CI 1.01–1.33,  $p=0.040$ ) were independently associated with ICU mortality.

**Conclusion:** Non-resolving pneumonia after several antibiotics lines without inflammatory syndrome, associated with progressive dyspnea, salty bronchorrhea, and lobar swelling (i.e. fissural bulging, compressed bronchi and vessels) were suggestive of P-ADC. Delayed diagnosis of diffuse P-ADC seemed an independent prognostic predictor and disease timely recognition may contribute to prognosis improvement.

**Comment 3:** Third, in the introduction part, the authors overstated the research question “assess the determinants of ICU and in-hospital mortality” because of the small sample size, the current study has very limited ability to answer this question. In this part, the authors provide insights on why “its treatment and prognosis may be substantially different from those of ARDS with common risk factors” because this is an important rationale of the current study topic.

**Reply 3:** We thank the reviewer for this comment. We agree that the small sample size limit the ability to predict mortality with good performance. However, we tried to restrict the number of variables entered in the models according to the “Peduzzi rule” (Peduzzi P, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol.* 1995 Dec;48(12):1503-10.), and renouncing to accurate precision of mortality we sought to adjust the variable “time to diagnosis” (our tested association) with other variable of severity of the clinical presentation at ICU admission (e.g. SAPS2, need for mechanical ventilation). Hosmer-Lemeshow goodness of fit tests indicated

good calibration in both models. The rarity of the disease remains also a major obstacle to prospective or large sample-size studies. However, we discuss the obvious limit in our model in terms of discrimination in the discussion section.

For the second part of the comment N°3 “In this part, the authors provide insights” we are not sure to understand a need for modification and we suppose that the word “should” could have been omitted by the reviewer before “provide insights”. Thus, we reinforce the notion that “P-ADC treatment and prognosis may be substantially different from those of ARDS with common risk factors”. We sincerely apologize if we did not understand well this comment.

**Changes in the text (Introduction):** Moreover, its treatment and prognosis may be substantially different from those of ARDS with common risk factors. Indeed, in comparison with ARDS of common causes, malignant ARDS has been demonstrated with high risk of ICU mortality (up to 96%) [8] and diffuse P-ADC may benefit from early administration of anti-cancer treatments.

**Changes in the text (Discussion):** First, this was a retrospective study, which involves a potential bias in patients’ selection or data collection, and the small number of subjects limited the performance (discrimination) and thus the interpretation of the multivariate analyses

**Comment 4:**Fourth, in the methodology part, the authors need to consider whether it is appropriate to design this study as a retrospective observational cohort study, because of the small sample size. I feel case series of 24 cases is more suitable. Because in statistics, factors associated with mortality of the 24 cases are an important focus of this study, but the total numbers of in-hospital and ICU deaths are only 15 and 6, respectively. Such sample can not, absolutely, provide a reliable and stable evidence on the associations of interest. In statistics, please indicate the P value of statistical significance.

**Reply 4:** We thank the reviewer for his comment and agree with the expected weakness of our mortality predictions models restricted to 3 variables, in terms of accuracy (AUC ROC). However, we formulated what we sought an important clinical hypothesis which is “a delayed diagnosis may unfavorably influence mortality in these patients”. This hypothesis, if confirmed, justified the exhaustive clinical description of the cases performed to provide the community with diagnostic clues. Renouncing to accurate precision of mortality, we rather sought to adjust the variable “time to diagnosis” (our tested association) with other variable of severity of the clinical presentation at ICU admission (e.g. SAPS2, need for mechanical ventilation). This have been notified in the revised version of the Statistics section. We thus restricted the number of variables to the number of events. A p values < 0.05 were considered statistically significant and Hosmer-Lemeshow goodness of fit tests indicated good calibration in both models (see supplements). As suggested by the reviewer we modified in the text the design of the study to “observational case series” rather than” retrospective observational study”.

**Changes in the text (Study design): Study design and setting.** This observational

case series study was conducted...

**Changes in the text (Statistics):**

Variables were compared with Mann-Whitney test for quantitative variables and chi-square test or Fisher exact test for qualitative variables. All tests were two-sided and p values < 0.05 were considered statistically significant. Because of the small sample size, a maximum of three variables identified with a p-value less than 0.20 in univariate analyses, and/or clinically relevant (including time between first symptoms and diagnosis – the tested hypothesis –) were included in a multivariate logistic regression model

**Reviewer B**

**Major comment**

**Comment 1:** Please describe the BAL technique in detail.

**Reply 1:** We thank the reviewer for his comment that give us the opportunity to precise the BAL technique that we use in our center. We used 50 ml of room temperature, sterile 0.9% saline injected via handheld 50 ml syringe, this repeated 4 times to reach a total of 200 ml instilled in the lungs. If only 5% of each 50 ml saline injected returns, this indicates that most of the injected saline will be retained in the lung and the procedure is immediately stopped. A return sample yield of 20% or more of the instillate is considered an adequate return (especially in the ICU setting), of which at least 10 ml is send for the cytological analysis. Instillate return is obtained manually, and a tubing is added to the handheld syringe for more “flexibility” during the procedure. BAL is generally performed in the right middle lobe or the lingula focal/patchy lung involvement, the site of BAL is guided by the Chest CT findings.

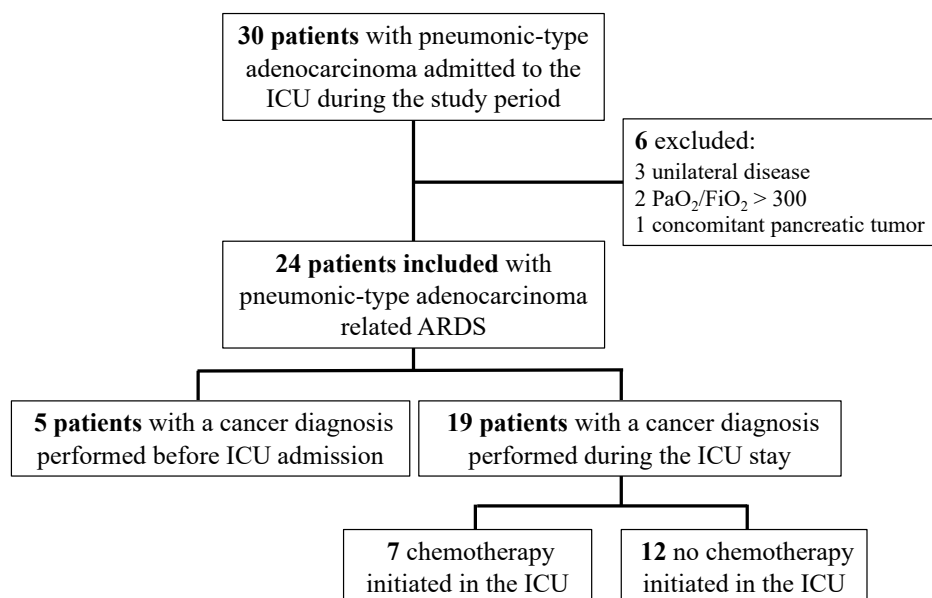
We thus added this sentence in the revised version of the manuscript (Methods section):  
“All histological (trans-bronchial biopsy, open-lung biopsy and autopsy) and cytological (sputum examination, bronchial aspirate, broncho-alveolar lavage (BAL)) samples were reviewed by experienced lung pathologist (M.A.) and cytologist (A.F.) and histological samples of patients admitted before 2011 were re-classified according

to current classifications [11, 14]. For the BAL procedures we used 50 ml of room temperature, sterile 0.9% saline injected via handheld 50 ml syringe, this repeated 4 times to reach a total of 200 ml instilled in the lungs.”

**Comment 2:** The authors showed a flowchart of patients in Figure 1. Did 5 patients had already been diagnosed with P-ADC-related ARDS or P-ADC only? In the manuscript, it is stated where the patients were transported from, but not in the flowchart. why is hospital mortality stated in Figure 1?

**Reply 2:** We thank the reviewer for these comments. Indeed, among the 24 patients included in the study, a diagnostic of Pneumonic-type adenocarcinoma was performed before the ICU admission in 5 patients. The text in the flowchart of the initial version was not sufficiently clear and we apologize for that. We sought to report hospital mortality in the subgroup of 19 newly diagnosed patients in order to provide the reader with a quick visual information on outcomes. We are no longer convinced by the relevance of mortality information on a flowchart. Thus, as suggested by the reviewer we modified the Figure 1 in the revised version of the manuscript taking into account these two comments as follows:

**Figure 1 (revised). Flowchart**



The Figure 1 (flowchart) was misreferenced in the main text as the reader could expect to observe information regarding the origin of the transfer. This information is not reported in the flowchart. We thank the reviewer for having pointed this mistake and we modified the beginning of the Results section of the revised version of the manuscript as follows: “The flowchart of the study is represented in the Figure 1. During the study period, 24 patients with P-ADC related ARDS were referred to our ICU and thus included. These admissions resulted in transfer from the respiratory wards (n=13; 54%), the emergency services (n=6; 25%) or other ICUs (n=5; 21%).”

**Comment 3:** Please make tables for multivariate logistic regression analysis for ICU and in-hospital mortality.

**Reply 3:** We thank the reviewer for this suggestion and thus we added a new Table 3 in the revised version of the manuscript that corresponds to the multivariate analysis of factors associated with ICU and hospital mortality.

**Table 3. Multivariate analysis of factors associated with intensive care unit (ICU) and hospital mortality.**

Variables	Prediction model of ICU mortality		Prediction model of Hospital mortality	
	OR (95%CI)	P value	OR (95%CI)	P value
<b>Time between first symptoms and diagnosis</b> (per day)	1.02 (1.00–1.03)	0.046	-	ns
<b>Simplified Acute Physiology Score 2</b> (per point)	1.16 (1.01–1.33)	0.040		
<b>Need for mechanical ventilation</b>	-	ns		
<b>Heart rate</b> (per point)			1.07 (1.00–1.15)	0.041
<b>Impossibility to dispense chemotherapy at any</b>			17.57 (1.19–)	0.041

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OR, odds ratio; CI, confidence interval; ICU, intensive care unit; ns, non-significative  
Dashes signifies that the variable has been proposed but excluded from the stepwise procedure.

\*As guidelines recommend not to repeat information between text and tables/figures we remove the text related to multivariate analysis results as follows (Results section, Mortality): “Multivariate analysis of factors associated with intensive care unit (ICU) and hospital mortality are reported in **Table 3**. More details about the variables selected, and the goodness-of-fit of the models are available in electronic supplement ES8. Neither the type of P-ADC (IMA or LPA) nor the mucinous feature was associated with ICU (p=0.68 and p=0.46 respectively) or in-hospital (p=0.68 and p=0.46 respectively) mortality.”

\*We also reordered the Tables citation in the text.

**Comment 4:** The authors conclude that the time between first symptoms and diagnosis is a significant factor associated with ICU mortality. However, the results of the multivariate analysis using the stepwise method are questionable—the reason is that patients diagnosed before being admitted to the ICU were mixed with those diagnosed after. Would the results be similar if you analyzed a group of 19 newly diagnosed patients?

**Reply 4:** We thank the reviewer for this comment. Indeed, the diagnosis of cancer was performed in 5 patients before the ICU admission. We agree that the time required to confirm the diagnosis for the 19 remaining newly diagnosed patients may have a different influence on mortality prediction. Days outside the ICU and days inside the ICU have certainly different clinical influence. However, for the 19 newly diagnosed

patients the diagnosis of cancer was performed in the ICU but generally during the first day of admission (median time between ICU admission and cancer diagnosis 1 (1–4) days) thus we considered the variable time between first symptoms and the cancer diagnosis as a pre-ICU admission variable for all patients. Moreover, multivariate analysis on a subgroup of patients in this study of low sample size, further limits its feasibility (only 3 ICU deaths and 6 hospital deaths). Indeed, exploratory analysis performed on the subgroup of 19 newly diagnosed patients showed that the time between first symptoms and cancer diagnosis seemed higher in ICU deaths (360 [185–460] days) in comparison with ICU survivors (210 [86–245] days) but the p-value did not reach statistical significance ( $p=0.169$ ). Regarding hospital mortality, the time between first symptoms and cancer diagnosis seemed also higher in hospital deaths (302 [163–395] days) in comparison with hospital survivors (180 [58–245] days) but the p-value did not reach statistical significance ( $p=0.105$ ).

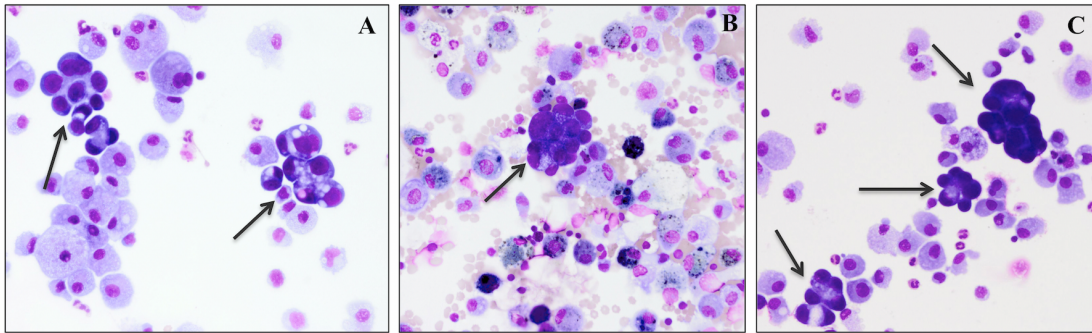
**Comment 5:** Although the manuscript states cytological findings in Table 2, it only lists cell fractions. Were the agglomerated neoplastic cells (type II pneumocytes or Clara cells) claimed by the authors found in all patients?

**Reply 5:** We thank the reviewer for this comment that gives us the opportunity to precise how the diagnostic of cancer is performed when based on cytological analysis in the clinical setting of suspected diffuse pneumonic type adenocarcinoma. Based on our experience, in some patients (8 [33%] in our study) the diagnosis is based on cytological specimen generally because histological samples are judged at high risk (e.g. transbronchial biopsy) in patients in whom bronchial biopsy (a safe procedure) rarely provide the diagnosis (distal lung disease). In these patients the identification of clusters of agglomerated neoplastic cells is strictly mandatory to affirm the diagnosis of P-ADC. A cytological diagnosis could not be affirmed just based on the identification of isolated atypical type 2 pneumocytes. This means that such agglomerated neoplastic cells (so called “morula” by some cytologists) were identified in 100% of patients in whom the diagnosis has been provided based on BAL analysis.

Below, see 3 examples of “neoplastic morulas” in 3 different patients (Figure 3 of the



article).



\*We thus added this sentence in the Methods of the revised version of the manuscript: “The cancer diagnosis could be confirmed based on cytological analysis (e.g. BAL), only if at least one agglomerate of neoplastic cells forming typical cytological features of P-ADC was identified. Details on pathological definitions are available in the electronic supplement ES2.”

\*References and details regarding cytological and histological findings are more reviewed in the ES2.

**Comment 6:** One of the results, in-hospital mortality, is not sufficiently discussed.

**Reply 6:** We thank the reviewer for this suggestion and totally agree with the fact that we did not sufficiently discuss in-hospital mortality in the initial version of the manuscript. We thus added this paragraph in the revised version of the discussion (Outcomes section):

**“Outcomes: comparison with existing data**

The 63% hospital mortality observed in our study seemed substantially higher than the 36% hospital mortality observed in a cohort of 446 lung cancer patients requiring ICU admission for mixed medical and surgical reasons [35]. However, this mortality bordered on the 54% hospital mortality of patients with lung cancer admitted for medical reasons (mostly acute respiratory failure) [36] and reached that observed in 1,004 cancer patients with ARDS criteria (64%) [4].”

**Minor comment**

**Comment 7:** Is ALP in diagnosis in Table S2 a misnomer for LPA?

**Reply 7:** We thank the reviewer for having pointed this typo and apologize for the mistake. We provided modification in the revised version of the Table S2.