Author’s response to reviews

Title: A rise in mean platelet volume during hospitalization for community-acquired pneumonia predicts poor prognosis: a retrospective observational cohort study

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Responses to the comments

Reviewer 1 (Anna Maria Azzini, M.D.):

"Really an original investigation, in particular because it considers also MPV changes during time. In this way it could be validated as a severity and/or prognostic biomarker to monitor CAP evolution during treatment."

We are grateful to Reviewer 1 for the statements regarding our manuscript.
"Only two questions:

1. Why did you consider death of any cause at 3 years after the acute episode?"

We agree with the Reviewer that evaluation of short-term mortality is most relevant to the purpose of our study. Yet, high long-term mortality has been reported among patients with community-acquired pneumonia (see reference 18). In addition, rising MPV during hospitalization in an internal medicine ward or for acute myocardial infarction was associated with increased long-term mortality (see references 13 and 15, page 11 of the Discussion section). Thus, we believe that analyzing long-term survival is also relevant.

"2. How do you explain (or try to explain) this strong correlation between high/rising MPV value and long-term mortality? High or rising MPV value, in the absence of hematological disorders could be the expression of severe inflammatory status, consequent to an acute infective syndrome. How it could influence death after a 3 years-period?"

We appreciate this comment. Indeed, the underlying pathophysiological mechanisms for a relationship of rising MPV with increased long-term mortality are unclear. We suggest that the main explanation is increased activation of enlarged platelets, which may persist after acute infective syndrome and result in an increased risk of thrombosis and decreased immune defense. Following the reviewer's comment, we have modified the appropriate paragraph of the Discussion section (pages 11-12 of the new version of the manuscript).

Reviewer 2 (A. Ariani)

"In this manuscript the Authors verified if a MPV increasing has a prognostic value in patient affected by CAP. In particular they assessed both the hospital and long-term survival. The paper is well written, the aim, methods and results are clear and the key message could be relevant even for clinical practice. The discussion is quite complete with likely hypothesis explaining the findings."
We are grateful to Reviewer 2 for the positive words concerning our manuscript.

Minor comments

"1. Methods: chronic inflammatory diseases (rheumatoid arthritis, polimyalgia etc) were not excluded but they influence the MPV. Do the Authors consider this point as a bias?"

We agree with the Reviewer that chronic inflammatory diseases may influence the MPV. However, the main aim of our study was to investigate clinical characteristics and the prognostic significance of changes in MPV in an acute inflammatory state such as hospitalization for pneumonia. We suggest that the rapid time-dependent MPV changes are more likely related to acute inflammation and possibly to other contributing factors (see the relevant paragraph of the Discussion section, page 10) than to chronic inflammatory diseases. Thus, we do not consider this point as a bias.

"2. Results: do the Authors verified if the ΔMPV was related with the some conditions (diabetes, CAD, lung or disease). In other words why are they so sure that ΔMPV is not an independent predictor of prognosis? Why do they consider MPV rise a "powerful" predictor? This point should be clarified in the discussion section."

We are grateful to the Reviewer for this comment. We agree that MPV changes may be related to certain variables (see Table 1 and the relevant paragraph of the Results section, page 6). To verify the prognostic significance of the ΔMPV, we performed multivariate analysis of variables that were associated with poor prognosis on univariate analysis (advanced age, male sex, rise in MPV, MPV > 8.5 fL at discharge, anemia, renal dysfunction, diabetes mellitus, coronary artery disease, chronic lung disease, heart failure, cerebrovascular disease, history of malignancy, hyponatremia, hypoalbuminemia, and higher CURB-65 and PSI scores – see page 8). On stepwise logistic regression analysis for in-hospital outcomes, a rise in MPV was one of the variables that most significantly predicted treatment with mechanical ventilation and in-hospital death (Table 2). Reevaluation by the Cox proportional-hazards model of variables that were found to be associated with decreased survival using the Kaplan-Meier method showed that a rise in MPV remained one of the most significant predictors of shortened long-term survival (Table 3). Thus, a rise in MPV may be considered as a powerful predictor of poor prognosis in
our patients. We suggest that our statement regarding changes in MPV as "a powerful predictor of poor prognosis" is more appropriate than as "an independent predictor of prognosis", because a possible relationship between ΔMPV and other predictors cannot be completely excluded. Following the reviewer's comment, we clarified this point in the Discussion section (pages 10-11 of the revised version).

"3. Conclusion: Results show that MPV rise is less important predictor than other anamnestic data (e.g. renal, cardiac, pulmonary and cerebrovascular affection). So why they suggest to use the MPV to improve patients risk stratification?"

We completely agree with this comment. Indeed, rising MPV was the most powerful predictor only for in-hospital death. Increased long-term mortality was less strongly predicted by a rise in MPV than by advanced age, cerebrovascular disease and higher PSI and CURB-65 scores. However, our results showed that ΔMPV ≥0.6 fL remained one of the variables most significantly associated with shortened survival (Table 3). Compared to other powerful predictors of poor prognosis that were determined at hospital admission, the ΔMPV reflected dynamic MPV changes throughout hospitalization. Thus, we suggest that repeated assessment of a simple routine parameter such as MPV during hospitalization may provide additional prognostic information and improve risk stratification for CAP patients. We briefly related to this point in the Discussion section of the revised version (pages 10-11).