Dear Reviewer,

Thank you very much for your comments. Enclosed is our revised manuscript and answers to the comments.

1. Explain why the information obtained with this study will change the course of the patient’s identified.

This causal translational research study will not affect the outcome of studied patients (this is a non-intervention epidemiologic study) but will help in better understanding the clinical pathogenesis of ALI/ARDS and the design of future ALI/ARDS prevention strategies. Since the therapeutic options are limited once ALI/ARDS develops, the prevention is paramount. Unfortunately, effective prevention interventions do not currently exist, and our knowledge about clinical pathogenesis of ALI/ARDS is limited. A large knowledge gap persists because we have a limited understanding why some patients with sepsis, trauma, pneumonia and shock do and others do not develop ALI/ARDS. By identifying patients at high risk earlier (in the emergency department and operating room), and collecting biospecimens and clinical data before ICU admission we hope to improve our understanding of ALI/ARDS clinical pathogenesis and identify targets for future quality improvement interventions and ALI/ARDS prevention trials.

Previous studies have concentrated on patients in the ICU with already established ALI/ARDS Hence the inferences from these studies with regards to ALI pathogenesis and potential prevention targets are limited.
2. What therapies could be offered to these patients that will affect the course of their disease?

Potential future prevention strategies include, but are not limited to 1) quality improvement interventions to limit specific hospital acquired exposures (delayed treatment of infection and shock, aspiration triggers, high tidal volume ventilation, plasma transfusion from alloimmunized donors), and 2) the use of systemic and inhaled anticoagulants, antiplatelet agents, anti-inflammatory drugs and antioxidants. Some of these therapies have already been tested in preliminary clinical trials with encouraging results [1-3]. This is in contrast to uniformly negative results of mechanistic interventions when applied later in the course of illness, once ALI/ARDS is established.

