Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

potentially in error because it does not consider that approximately 80% of patients in both arms were receiving remdesivir, another antiviral therapy. Antibodies active against SARS-CoV-2 in CCP function as antivirals,[2] which means that, for most patients in PassITON, CCP was assessed as an add-on combination therapy with another antiviral agent. Hence, the absence of a favorable effect for CCP in PassITON may simply reflect an non-significant incremental effect of combination therapy rather than a shortcoming for this antibody therapy. Indeed, the Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients (CONTAIN COVID-19)[3] and O'Donnell et al[4] trials published in 2021 demonstrated CCP efficacy in the reduction of mortality rates for patients who were hospitalized early in the pandemic before remdesivir became part of standard clinical practice. It is notable that an analogous negative result for antibody-drug combination therapy was also observed in the early antibiotic era when physicians added sulfonamides to convalescent serum to try to improve the outcome of pneumococcal pneumonia.[5] Because serum or sulfonamide monotherapy were each effective against pneumococcal pneumonia, there was likely no opportunity for improvement when they were combined.

We recognize that this trial was conducted at a time when therapeutic approaches were changing rapidly and remdesivir and corticosteroids were introduced as standard of care; investigators could not have controlled for these shifting variables while providing optimal patient care. Nevertheless, the results should be interpreted in the context of known biologic effects and published clinical experience. Given the concerns about concurrent remdesivir use, the current PassITON analyses on CCP efficacy are inconclusive.

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Response

To the Editor:

We appreciate the dialogue about the Passive Immunity Trial for Our Nation (PassITON) stimulated by letters to the editor from Casadevall and Henderson, Shoham and Focosi, and Senefeld et al. PassITON was a multicenter, blinded, placebo-controlled randomized clinical trial that evaluated the efficacy of COVID-19 convalescent plasma added to usual care among 960 adults who were hospitalized with COVID-19 at 25 hospitals in the United States.[1] Key findings from PassITON included null results for convalescent plasma compared with placebo for clinical status (illness severity on an ordinal scale) 14 days after randomization (adjusted OR, 1.04; 1/7 support interval, 0.82-1.33) and for 28-day mortality rates (adjusted OR, 1.04; 1/7 support interval, 0.69-1.58).

Casadevall and Henderson note that convalescent plasma vs placebo in PassITON was added to usual care therapies for COVID-19; thus, the trial did not provide insight into the efficacy of convalescent plasma alone in the absence of other COVID-19 treatments. In PassITON, participants were not treated with concomitant passive antibody therapies (such as anti-SARS-CoV-2 monoclonal antibodies, hyperimmunoglobulin, or open label convalescent plasma). However, PassITON participants were permitted to receive non-immunologic COVID-19

therapies at the discretion of their treating providers; during the same hospitalization as PassITON enrollment, approximately 79.5% of participants received remdesivir, and 89.4% of participants received corticosteroids, which is consistent with usual care practices at the participating hospitals. Our goal was to understand the efficacy of convalescent plasma added to routine (usual care) treatment for hospitalized adults with COVID-19 because we believed this was the most relevant question for clinical decision-making.

Shoham and Focosi note that PassITON enrolled patients across the full spectrum of disease severity for hospitalized COVID-19, including patients treated at baseline (randomization) without supplemental oxygen (9.2%), standard flow oxygen (55.9%), high-flow nasal oxygen or noninvasive ventilation (21.9%), and invasive mechanical ventilation or extracorporeal membrane oxygenation (13.0%). Our primary analysis included patients across this full spectrum of disease severity. Our subgroup analyses, which were underpowered to draw definitive conclusions, did not suggest evidence of benefit for convalescent plasma among patients with lower baseline severity of illness (Figure S3 in the primary manuscript) or shorter duration of illness (Figure S3 and Figure S9 in the primary manuscript). Shohom and Focosi further note that 50 of 463 of the convalescent plasma units (10.8%) that were used in PassITON did not have neutralizing activity above the threshold that we considered as demonstrative of neutralizing function.[2,3] It is important to note that all convalescent plasma units used in PassITON met criteria for "high titer" based on a binding assay measurement, which is, by far, the most common method to describe the composition of convalescent plasma. Most convalescent plasma trials relied only on binding assays to describe the concentration of antibodies.[4,5] In PassITON, we went a step further and also described the neutralizing activity of anti-SARS-COV-2 antibodies in the plasma that we used; these analyses showed that 89.2% of the plasma units had confirmed neutralizing activity (in addition to high-binding antibody titer). A sensitivity analysis that excluded patients who were treated with convalescent plasma without confirmed neutralizing activity was consistent with the primary intention-to-treat results.

Senefeld et al note that COVID-19 convalescent plasma may have the most potential for benefit when used very early after onset of symptoms, such as within the first 3 days. Most patients who are hospitalized for COVID-19 are not admitted within this time window. A common course of illness for patients who ultimately are hospitalized for COVID-19 is several days of symptomatic illness, then clinical deterioration results in hospital admission. The primary question addressed in PassITON was whether administration of convalescent plasma shortly after hospital admission was beneficial. Thus, we thought it was important to include patients in the trial who had the typical course of illness that leads to hospitalization (ie, several days of symptoms and then clinical deterioration). We also recognized that the probability of efficacy was low for patients who had very prolonged duration of symptoms. Balancing the desire to include a majority of patients who were hospitalized for acute COVID-19 (to maintain applicability to the hospitalized COVID-19 population) and the desire to exclude patients highly unlikely to benefit from convalescent plasma because they were already in a later stage of illness not driven by viral replication, we decided to include patients in PassITON who had up to 14 days of symptoms. To supplement the primary analysis, we performed heterogeneity of treatment effect analyses evaluating the interaction between symptom duration and efficacy. The median (interquartile range) duration of symptoms prior to randomization was 8 (5 to 10) days. Overall results, which included all enrolled patients with 0 to 14 days of symptoms, for the primary outcome were null, with the point estimate favoring placebo over convalescent plasma (adjusted OR, 1.04; 1/7 support interval, 0.82 to 1.33). In the subgroup of participants with symptom duration $\leq$ 5 days, there was no suggestion of efficacy; the point estimate for the primary outcome favored placebo over convalescent plasma (adjusted OR, 1.16; 1/7 support interval, 0.74 to 1.82). Furthermore, when we considered duration of symptoms prior to randomization on a continuous scale, there was no evidence of interaction between symptom duration and efficacy (Figure S6 in the primary manuscript), which meant that the data did not suggest greater efficacy for patients with shorter duration of symptoms.

In summary, we believe PassITON provides robust data that add to the growing body of evidence that the administration of COVID-19 convalescent plasma at the time of hospital admission is not beneficial for most patients with acute COVID-19. Although the trial was underpowered for subgroup analyses to provide definitive results (which is very common for clinical trials), the available data suggest no benefit from convalescent plasma for patients with less severe in-hospital disease (such as treated with no

oxygen or standard flow oxygen) and patients with a short duration of illness (such as ≤ 5 days). These results are disappointing because COVID-19 convalescent plasma could be readily available throughout the world and potentially could evolve along with genetic changes in the virus, thereby alleviating the problem of new SARS-CoV-2 variants being less susceptible to monoclonal antibody therapies that were developed earlier in the pandemic.[6] But we must practice evidence-based medicine. Despite the appeal of COVID-19 convalescent plasma being biologically rational and widely available, the evidence informs us that it is not an efficacious treatment for most hospitalized patients with moderate-to-severe COVID-19.

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COPD Risk After Military Service

Let's Go Further Before Concluding

To the Editor:

We read with great interest the article in *CHEST* (October 2022) by Trupin et al,[1] who attempted to assess the impact of inorganic dust inhalation during military service on the occurrence of COPD in veterans. The authors conclude that military service should be considered by clinicians in evaluating a patient's occupational history. However, as the authors state, their job exposure matrix that was used to estimate inorganic dust exposure during military service, which described in more detail in a previously published work,[2] does not take into account the likelihood of exposure to other dusts (such as from organic materials), gases, fumes, or vapors. Burn pit emissions and desert dust exposure nevertheless are two major sources of respiratory health impairment.[3] Furthermore, the study of only veterans who were followed by the Veterans Affairs Department introduces a major recruitment bias because a many of the veterans are not or no longer followed by this Department. Finally, the authors do not mention the criteria by which the diagnosis of COPD is established. Over the last 10 years, the Global Lung Function Initiative has highlighted the need to review the theoretic diagnostic values of airflow limitation for the diagnosis of COPD. Although age and sex vary the figures, ethnicity is a very important factor to be taken into account so that an incorrect diagnosis of COPD will not be made.[4] The use of the Global Lung Function Initiative recommendations could have important diagnostic consequences, especially in non-