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16 December 2016

Dear Editor,

In reply to: "Meyer CP, et al. The association of hypoalbuminemia with early perioperative outcomes – A comprehensive assessment across 16 major procedures"

We read with interest the recent work by Meyer and colleagues (1). In this study, utilising data from the ACS-NSQIP database, the presence of pre-operative hypoalbuminemia was associated with adverse outcomes across a number of major surgeries. Taking those undergoing colectomy as an example, controlling for covariates such as gender, race, comorbidity indices and BMI, a serum albumin<3.5g/dl was associated with increased risk of post-operative complications (adjusted odds ratio (OR) 1.41), blood transfusion (OR 1.32), prolonged length of stay (OR 1.71) and mortality (OR 2.29) (all $P<0.001$). Similar results were observed across a number of other oncological, cardiovascular and orthopedic procedures. These results largely mirror those of Gibbs and colleagues who, utilising the National VA Surgical Risk Study database, found that a decrease in serum albumin from 4.6g/dl to 2.1g/dl was associated with an exponential increase in 30-day mortality from <1% to 28% (2). Risk of post-operative morbidity similarly increased.

Although proposed as a marker of nutrition, hypoalbuminemia in the present study is unlikely to reflect poor nutritional status. Serum albumin correlates poorly with clinical assessment of nutritional status (3), and in states of malnutrition, serum albumin concentrations are often maintained at the expense of other sources of protein such as skeletal muscle (4). In

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such circumstances, hypoalbuminemia is a late, often pre-terminal occurrence. Therefore, given that only 5% of patients with hypoalbuminemia in the present study had a BMI<18.5, it is unlikely that this is the primary mechanism responsible for the present associations with adverse outcome.

Albumin has long been recognised to be a negative acute phase reactant, circulating concentrations reflecting, in part, the magnitude of the systemic inflammatory response (5). More recently, it has become apparent that markers of the systemic inflammatory response such as C-reactive protein and neutrophil count have a strong independent association with cancer specific (6) (7) and overall (8)mortality.

Although alluded to by the authors in their discussion, it is important to note that the results of their surgical mortality study (1), and that of Gibbs and colleagues (2), fail to control for the important confounding effect of the systemic inflammatory response. Moreover, whether hypoalbumaemia is mainly the result of a nutritional deficit or secondary to a systemic inflammatory response is of considerable importance since the former would suggest that nutritional intervention may be beneficial. In contrast, if the latter was dominant then it would suggest an anti-inflammatory intervention may be beneficial.

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Irrespective, it is clear that if albumin is being monitored then a marker of the systemic inflammatory response such as C-reactive protein should also be monitored. Indeed, work by our group over the past decade or so has identified the prognostic value of the combination of C-reactive protein and albumin in patients with cancer and with chronic disease (8-10). This systemic inflammation based prognostic score (termed the modified Glasgow Prognostic Score, mGPS, Table 1), has been shown to have consistent prognostic value in a variety of clinical scenarios. We recommend such an approach in the analysis carried by Meyer and colleagues.

Yours sincerely,

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Table 1 – The modified Glasgow Prognostic Score

Score	Determinant
mGPS 0	CRP ≤10/mg/L
mGPS 1	CRP >10/mg/L
mGPS 2	CRP >10/mg/L and Albumin <35g/L

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