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Letter in Response to ''No Cytokine is an Island: IL-6 Alone is Not Enough to Predict the Morbidity After Major Abdominal Surgery''

To the Editor:

We thank Dr Moris et al for their interest in our paper and their inspiring views on the interaction between the postoperative immune response and the development of complications after surgery. Dr Moris et al raise an important point. The postoperative inflammatory response is much more complex than an increase of interleukin (IL)-6 and C-reactive protein (CRP) levels. Surgery elicits a proinflammatory response, which is at the same time counterbalanced by immunosuppression.[1] In addition, Dr Moris et al are right to emphasize that other systems, such as the hypothalamic-pituitary-adrenal axis, are involved as well. Although our multivariate analysis was not primarily designed to identify independent risk factors for postoperative complications, this is also supported by our results since the use of renin-angiotensin aldosterone system (RAAS) inhibitors was associated with worse outcome.[2]

Our study is not an in-depth analysis of the complex process of immune activation after surgery. Measuring levels of other pro and anti-inflammatory cytokines, fibrinogen, and hormones involved in the activation of the immune system would have provided more insight in this topic. However, for financial and practical reasons, we chose to study a select number of cytokines based on previous research.[3,4] Our results do provide a strong incentive to perform a meticulous analysis on this issue, because levels of IL-6 on day 1 were predictive and independently associated with worse outcome, and therefore may be a therapeutic target.

As Dr Moris et al describe, there are many factors that can influence the immune response after surgery. For example, immune function may be better preserved after laparoscopic than open surgery.[5] In our study population, patients with a laparoscopic approach had lower levels of IL-6 (242 [interquartile range (IQR) 63–543] vs 390 [IQR 256–737] pg/ml; $P < 0.006$) and CRP (74 [IQR 56–95] vs 96 [IQR 61–149] mg/L; $P < 0.004$) on day 1 and a lower leukocyte count on day 3 (9.0 [IQR 7.0–11.0] vs 10.5 [IQR 8.1–13.1] 10^9/L; $P < 0.024$) and day 7 (8.0 [IQR 6.8–10.9] vs 10.8 [IQR 8.9–16.3] 10^9/L; $P < 0.001$) compared with patients with open surgery. Levels of tumor necrosis factor (TNF)-α were unaffected by the surgical approach.

Dr Moris et al suggest that malignancy may be related with a reduced immune response after surgery. We did not find such an association. Patients with malignancy had increased levels of IL-6 on day 1 (373 [IQR 208–662] vs 274 [IQR 48–689] pg/mL; $P < 0.039$) and lower levels of TNF-α on day 3 (0 [IQR 0–0.9] vs 0.8 [IQR 0.3–2.9] pg/mL; $P < 0.001$). Leukocyte count and levels of CRP were comparable between patients with and without malignancy.

We agree that underlying liver disease and intraoperative ischemia/reperfusion injury caused by the Pringle maneuver or aortic cross-clamping may influence the postoperative inflammatory response.[6] Nevertheless, none of the patients suffered from relevant underlying liver disease. Similarly, aortic cross-clamping was not performed in our study patients. Nine patients did undergo hepatic surgery, which includes the Pringle maneuver. These patients had increased levels of IL-6 on day 3 (136 [IQR 98–545] vs 74 [IQR 34–160] pg/mL; $P < 0.013$) and day 7 (149 [IQR 53–442] vs 29 [IQR 14–103] pg/mL; $P < 0.048$), and decreased levels of CRP on day 1 (42 [IQR 25–63] vs 84 [IQR 60–111] mg/L; $P < 0.003$). Levels of TNF-α and leukocyte count were similar between the groups. Although 9 patients did not allow us to draw firm conclusions, the fact that patients undergoing hepatic surgery had similar levels of CRP on days 3 and 7 compared with patients undergoing nonhepatic surgery, despite increased IL-6 levels, may suggest that hepatic injury attenuates the ability to produce inflammatory markers such as CRP and predict poor outcome.[7]

In conclusion, levels of IL-6 are predictive of postoperative complications after major abdominal surgery and may improve clinical decision-making in the early postoperative period. The exact role of IL-6 in the pathogenesis of adverse outcome and whether IL-6 is a possible therapeutic target require further investigation.

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CRP Predicts Safe Patient Discharge After Colorectal Surgery

To the Editor:

We read the article by Giaccaglia et al[1] with great interest. In this study, the authors assess the potential benefit of procalcitonin (PCT) as a marker of anastomotic leakage after colorectal surgery. They conclude that PCT is a helpful biomarker for early diagnosis of anastomotic leakage after colorectal surgery and that results of furthers studies will tell if PCT and/or C-reactive protein (CRP) values might be added to discharge criteria after fast-track surgery.

We have several concerns about the methods. The authors designed a prospective observational study in 3 high-volume centers, in which 504 patients were included. However, the sample size calculation is not described. More generally, the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist should have been used to report this study.[2]

We also think that the results shown by the authors do not fully support their conclusion. Indeed, they found that the negative predictive values (NPVs) for anastomotic leakage with PCT were 96.9% (cut-off <2.7 ng/mL) and 98.3% (cut-off <2.3 ng/mL) in third and fifth postoperative days (PODs), respectively. With CRP, NPVs were 96.4% (cut-off <16.9 mg/mL) and 98.4% (cut-off <12.5 mg/mL) in third and fifth PODs, respectively. Based on these proposed cut-offs, positive predictive values (PPVs) were 34% and 32% for PCT, and 19.5% and 22.1% for CRP. So, when serum levels of PCT and/or CRP are under the cut-off proposed (ie, NPV), the occurrence of anastomotic leakage is not likely and patients can thus be safely discharged. The addition of PCT to CRP seems not cost-effective as the cost of PCT is higher and as the gain observed for NPV is only 0.5% in third POD. When serum levels of PCT and/or CRP are over the proposed cut-off (ie, PPV), the probability of occurrence of an anastomotic leakage is low for both markers (at most 34%). So PCT and CRP are not helpful for the early diagnosis of anastomotic leakage. For better interpretation of the results, we also would like to know what are the values of positive and negative likelihood ratios.

As stated by the authors, reliable markers for safe patient discharge are mandatory in the era of short-stay surgery. In this context, a reliable marker is defined by a high NPV, and CRP values seem to be enough. Unfortunately, the early diagnosis of anastomotic leakage remains difficult and cannot be predicted by a single biological marker.[3] The remaining question is so, how to manage patients with isolated high CRP level. Within the framework of short-stay surgery, continuous surveillance after discharge by use of messaging modalities and tele-monitoring might be helpful in these patients to avoid the failure to rescue.[4]

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CRP Predicts Safe Patient Discharge After Colorectal Surgery: Reply

Reply:

We would like to thank Aurelién Duprè, Johan Gagniér, Heloïse Samba, Michel Rivoire, and Karem Slim for their comments about our article "Procalcitonin Reveals Early Dehiscence in Colorectal Surgery: The PREDICS Study."[1] It is very rewarding to realize that this paper is stimulating so many observations, this means that we are talking about an interesting topic.[2]

Thank you for underlining that PREDICS is a large prospective observational study, involving 3 high-volume colorectal centers in Italy. It is to note that we described study methods in our first preliminary paper[3]; anyway, we are glad to share with you that sample size was calculated for a difference of at least 10% between the area under the receiver operating characteristics (ROC) curves (AUCs) of C-reactive protein (CRP) and procalcitonin (PCT). In the pilot study,[3] an AUC of 0.884 was observed for PCT at third postoperative day and used for the calculation. The prevalence of anastomotic leakage was assumed to be 14% according to the preliminary study, but was much lower in the PREDICS study data (5.6%). Total number of patients to include was estimated to be 441. The study was designed to have 80% power with an alpha error of 0.05.

Regarding strengthening the reporting of observational studies in epidemiology checklist,[4] we decided not to publish it because we consider it a useful tool only during study design; anyway, in the "Materials and methods" section, we carefully described all study characteristics (inclusion and exclusion criteria, variables reported in the database, and statistical analysis).

Positive and negative likelihood ratio (PLR and NLR) for PCT in third and fifth postoperative days (PODs) are, respectively: 7.14 and 0.44, and 9.9 and 0.33. For CRP, PLR and NLR in third POD are 3.26 and 0.50, and in fifth POD are 5.28 and 0.30, respectively. According to these results, usefulness of procalcitonin both in third and fifth POD is greater than CRP, confirming the results previously shown in our article with ROC curves. Therefore, according to PREDICS outcomes, together with this LR analysis, we keep stating that PCT and CRP could be usefully added as a diagnostic tool in early diagnosis of anastomotic leak (AL) in patients undergoing colorectal surgery for cancer. It should not absolutely be a fight between the 2 biomarkers, but a fight for better patient care. So, because adding PCT to CRP in fifth POD enhances AL diagnosis in a statistically significant way, we are proud to keep stating that this advantage is worth for patients' life. In fact, if the patient is discharged earlier and will do well at home, we save money; on the contrary, if AL is diagnosed early, it is possible to avoid sepsis and late reoperation, and try to pursue medical therapy saving money again, and—most important—avoiding longer