Reply to Letter: ''A Different Approach to the Use of C-reactive Protein and Procalcitonin in Postoperative Infectious Complications''

Reply:

We would like to thank Francisco Javier Medina-Fernandez and Cesar Diaz-Lopez[1] for their insightful and thoughtful considerations about our article ''Procalcitonin Reveals Early Dehiscence in Colorectal Surgery: the PREDICS Study.'' In the aim to analyze negative and positive predictive values (NPV and PPV) for anastomotic leak (AL) of C-reactive protein (CRP) and procalcitonin (PCT), we divided our study population in three groups: patients with AL, with complications other than AL, and with no complications. Effectively, within the patients with 'other complications,' we did not distinguish between infectious and noninfectious complications. Therefore, with the purpose of overcoming this bias, we reanalyzed the data.

As shown in Table 2 of our article,[1] a total of 92 patients (18.2%) had a postoperative complication, 28 of them (5.6%) anastomotic leak and 83 (16.4%) 'other' complication. Between the latter 83 patients, 33 had an infective (for example, pneumonia, wound infection, and urinary tract infection) and 50 had a noninfective problem, such as bleeding, pulmonary embolism, or myocardial infarction. It is to note that we registered a total of 68 noninfective complications, having 18 patients with more than one complication such as profuse bleeding and myocardial infarction or renal failure at the same time. In our analysis, patients having AL and other complications have been included in the AL group. Similarly, also patients having both infective and non-infective complication have been considered in the infective group. Using ANOVA with log10-transformed data and Tukey HSD post hoc comparisons, we did not find statistically significant differences between the two subgroups (infective complications but not AL vs other noninfective complications) regarding mean CRP and PCT values, except for CRP in third post-operative day (POD) ($P = 0.048$). Moreover, using logistic regression models to predict anastomotic leak, receiver-operating-characteristic curve for biomarkers are very similar to the ones already published. In fact, regarding the noninfective other complications, area under the curve (AUC) for PCT and CRP are respectively 0.743 and 0.783 (third POD) and 0.753 and 0.835 in fifth POD. When we use both biomarkers together, AUC is 0.826 in third and 0.827 in fifth POD. In the other infective complications, AUC for PCT and CRP are respectively 0.631 and 0.593 (third POD) and 0.729 and 0.743 in fifth POD.

Interestingly, we also didn't find any statistically significant differences between patients undergoing laparoscopic (group A) or open (group B) colorectal resection from cancer. In fact, between the 504 patients undergoing elective colorectal surgery, for malignant diseases, we registered 28 (5.6%) anastomotic leaks, 13 in Group A and 15 in Group B. In third POD, mean PCT values in patients undergoing laparoscopic surgery were lower compared with the laparotomic group, in the AL group, in the other complications group and in the 'no complication' group (4.24 vs 4.66 ng/mL, 2.12 vs 2.07 ng/mL, and 1.09 vs 1.14 ng/mL, respectively) but not in a statistically significant way ($P = 0.99$). Also in fifth POD, mean PCT values of patients with leak of Group A were lower compared with Group B (3.33 vs 5.02), but not in a statistically significant way ($P = 0.98$).

Moreover, to have an homogeneous population, and differently from our preliminary study,[2] we deliberately excluded all emergency procedures, avoiding all perforated and acutely infected patients, and included only elective cancer patients.

Regarding the reported disparities of CRP values, our recent study[1] showed similar results to the IMACORS study, also newly published on this journal.[3] In fact, Facy et al[3] used mg/L as unit of measure and we employed mg/dL; so their median CRP values in third POD for patients with infectious complications are very similar compared with ours (16.8 mg/dL for IMACORS vs 22 mg/dL for PREDICS). On the other hand, there are some disparities regarding PCT; in third POD median values in AL patients are 1.42 ng/mL for IMACORS versus 4.10 ng/mL in PREDICS. Conversely to PREDICS, in the IMACORS study also patients with diverticular disease (11.6%) and with inflammatory bowel disease (2.2%) have been recruited, so PCT is expected to be higher. Moreover, in PREDICS, 75% of patients underwent laparoscopic surgery versus nearly 30% in IMACORS, and this is another reason we would expect IMACORS procalcitonin levels to be higher, not lower. Nonetheless, would be very interesting to deeply understand the reasons of these disparities. It is to note that in both studies the same measuring system has been used (Brahms PCT Kryptor, Termo-Fischer Scientific, Hennigsdorf, Germany).

Moreover, we still think that PCT, with its earlier peak in first POD, might give a better help than CRP that peaks in second POD, because of early patients discharge protocols (quite often in third or in fourth POD) with increasing diffusion of laparoscopic and minimally invasive surgery.[4]

It would be also interesting to know if these biomarkers are working well in other surgical oncological fields, with appropriate studies, such as pancreatic cancer and stomach cancer. Currently there are two ongoing trials in our Institution about these topics.

The authors in their Letter also propose a new approach using patient's personal CRP values in second POD and comparing it with the biomarkers in the day of the suspected complication, as already published in their recent study, and suggesting to apply this protocol to PCT.[5] In literature has been reported that postoperative values of CRP in patients with no complications could be influenced by the surgical procedure and personal variability.[6,7] We think that the idea of using each patients threshold is brilliant, but, instead of remeasuring the biomarker when the complication is already suspected, perhaps it can be done before patients discharge to make it safer or to keep the patient for further studies.

Leaving on a side the discussions about different cuts-off and different methods of making the biomarkers measurement more efficient in predicting complications, the message that should come up is: biomarkers can help the surgeon in his/her daily practice, improving patients outcomes.

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