

management of clinically silent gallstones is not widely practiced outside of leading institutions and requires considerable investment in resources and team training, and sufficient volumes to maintain proficiency. The small likelihood of detecting clinically silent stones in general practices argues against intraoperative management becoming widely disseminated in lower or even intermediate volume hospitals where most cholecystectomies are performed. For these reasons, we felt inclusion of LCBDE and ERCP in the analysis was outside the scope of our study, which is directed at intraoperative detection in general surgical practices.

We agree with Dr. Date's comment that most general surgeons are not trained in IOUS. However, it has been reported that the learning curve for proficiency in IOUS is relatively brief and that when proficiency is achieved its sensitivity, specificity, and rate of successful CBD visualization is higher than IOC.³ Although not presented in our final article, using subordinate meta-analyses, we determined that the success rates for IOUS and IOC were 95% and 90%, respectively.^{4–10} It is thus difficult to reconcile the feeling that IOUS is hard to master (shared by many) with the available data. An additional point is that, in our study, a two-way sensitivity analysis was used to evaluate cost-effectiveness of IOUS, IOC, and EM at varying sensitivities and specificities of IOUS and IOC. The results showed that IOUS would always be preferred over IOC, in that it is less costly and more effective, at sensitivity/specificity levels between 0 and 1. If the sensitivity of IOUS were to fall below 27.2% and specificity below 90.2%, the model predicts that EM would be more cost effective. We also performed extensive sensitivity analyses on the costs of IOC, IOUS, and the management of symptomatic CBD stones. Our conclusion that for patients with a 9% risk for CBD stones, IOUS was superior to IOC and EM held true across variations in the costs of each of the management strategies. Based on these analyses, even for inexperienced but properly trained practitioners, IOUS would be cost-effective for detecting choledocholithiasis.

Date et al also discussed the use of routine preoperative Magnetic resonance cholangiopancreatography (MRCP) in the detection of asymptomatic choledocholithiasis. Although, it may be used in patients with high likelihood of CBD stones, routine use of MRCP have not been shown to be cost-effective or indicated in patients with asymptomatic stones or for patients who are at low risk for CBD stones (ie, those with no abnormal laboratory or radiologic findings).^{11,12}

Disclosure: The authors declare no conflicts of interest.

Susie X. Sun, MD
Department of Surgery
The Pennsylvania State University
College of Medicine
Hershey
PA

Department of Public Health Sciences
The Pennsylvania State University
College of Medicine
Hershey
PA

Affif N. Kulaylat, MD
Department of Surgery
The Pennsylvania State University
College of Medicine
Hershey
PA

Department of Public Health Sciences
The Pennsylvania State University
College of Medicine
Hershey
PA

Christopher S. Hollenbeak, PhD
Department of Surgery
The Pennsylvania State University
College of Medicine
Hershey
PA

Department of Public Health Sciences
The Pennsylvania State University
College of Medicine
Hershey
PA

David I. Soybel, MD
Department of Surgery
The Pennsylvania State University
College of Medicine
Hershey
PA

dsoybel@hmc.psu.edu

REFERENCES

1. Sun SX, Kulaylat AN, Hollenbeak CS, et al. Cost-effective decisions in detecting silent common bile duct gallstones during laparoscopic cholecystectomy. *Ann Surg*. 2015 [Epub ahead of print].
2. Collins C, Maguire D, Ireland A, et al. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited. *Ann Surg*. 2004;239:28–33.
3. Falcone RA Jr, Fegelman EJ, Nussbaum MS, et al. A prospective comparison of laparoscopic ultrasound vs intraoperative cholangiogram during laparoscopic cholecystectomy. *Surg Endosc*. 1999; 13:784–788.
4. Perry KA, Myers JA, Deziel DJ. Laparoscopic ultrasound as the primary method for bile duct imaging during cholecystectomy. *Surg Endosc*. 2008;22:208–213.
5. Machi J, Oishi AJ, Tajiri T, et al. Routine laparoscopic ultrasound can significantly reduce the

need for selective intraoperative cholangiography during cholecystectomy. *Surg Endosc*. 2007; 21:270–274.

6. Hublet A, Dili A, Lemaire J, et al. Laparoscopic ultrasonography as a good alternative to intraoperative cholangiography (IOC) during laparoscopic cholecystectomy: results of prospective study. *Acta Chir Belg*. 2009;109:312–316.
7. Li JW, Feng B, Wu L, et al. Intraoperative cholangiography in combination with laparoscopic ultrasonography for the detection of occult choledocholithiasis. *Med Sci Monit*. 2009;15: MT126–MT130.
8. Catheline JM, Turner R, Paries J. Laparoscopic ultrasonography is a complement to cholangiography for the detection of choledocholithiasis at laparoscopic cholecystectomy. *Br J Surg*. 2002;89:1235–1239.
9. Videhult P, Sandblom G, Rasmussen IC. How reliable is intraoperative cholangiography as a method for detecting common bile duct stones? A prospective population-based study on 1171 patients. *Surg Endosc*. 2009;23:304–312.
10. Tranter SE, Thompson MH. A prospective single-blinded controlled study comparing laparoscopic ultrasound of the common bile duct with operative cholangiography. *Surg Endosc*. 2003;17:216–219.
11. Jendresen MB, Thorboll JE, Adamsen S, et al. Preoperative routine magnetic resonance cholangiopancreatography before laparoscopic cholecystectomy: a prospective study. *Eur J Surg*. 2002;168:690–694.
12. Nebiker CA, Baierlein SA, Beck S, et al. Is routine MR cholangiopancreatography (MRCP) justified prior to cholecystectomy? *Langenbecks Arch Surg*. 2009;394:1005–1010.

Biomarkers Capable to Early Predict Postoperative Complications: The Grail

To the Editor:

We read the article by Rettig et al¹ on correlation between systemic inflammation and adverse outcomes after major abdominal surgery with great interest. The authors tested the predictive performance of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) in a cohort of 137 patients. Focusing on IL-6 on postoperative day 1 (POD1), the ROC curve identified an optimal cut-off of 432 pg/mL, which seems to be independently associated with complications in multivariate analysis. The authors concluded that a high level of IL-6 on POD1 was associated with complications and this may help to stratify patients. The identification of biomarkers capable to accurately predict complications during early postoperative phase remains a clear unmet need matter of debate. The study by Rettig

et al collecting such a prospective cohort is therefore very important.

Unfortunately, the surgical approach (laparoscopy or open) was neither reported nor included in the analyses. As laparoscopy has been evidenced to reduce surgical stress response and postoperative complications,^{2,3} this would be an important element. Therefore, integrating the surgical approach in their multivariate analysis could possibly change the statistical significances, and the conclusion. Moreover, it would be interesting to know why the authors did focus on IL-6, which is not a marker used routinely in clinical practice. Some comments on the potential limitations regarding reproducibility of the test and its cost would be of additional interest.

Ismail Labgaa, MD
Nicolas Demartines, MD, FACS
Martin Hübner, MD

Department of Visceral Surgery, University
 Hospital of Lausanne, Lausanne
 Switzerland
 demartines@chuv.ch

REFERENCES

1. Rettig TC, Verwijmeren L, Dijkstra IM, et al. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. *Ann Surg.* 2016;263:1207–1212.
2. Veenhof AA, Vlug MS, van der Pas MH, et al. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. *Ann Surg.* 2012;255:216–221.
3. Kennedy GD, Heise C, Rajamanickam V, et al. Laparoscopy decreases postoperative complication rates after abdominal colectomy: results from the national surgical quality improvement program. *Ann Surg.* 2009;249:596–601.

Biomarkers Capable to Early Predict Postoperative Complications: The Grail

To the Editor:

We thank Labgaa et al. for their interest in our article and welcome the opportunity to respond. As they correctly point out patients undergoing laparoscopic abdominal surgery have an improved outcome compared with patients with open surgery¹. This may be the result of a superior preservation of immune function, measured by higher human leucocyte antigen-DR expression on monocytes

after laparoscopic surgery.² Similarly, one might argue that laparoscopic surgery is associated with reduced postoperative levels of IL-6. Although prior reports have shown that levels of IL-6 on day 1 were similar in patients randomized to open or laparoscopic colorectal surgery if treated according to a fast-track protocol.^{2,3} Labgaa et al. suggest that including the surgical approach (laparoscopic vs open) in multivariate analysis may have changed the results of our study.⁴ In our study population, 69 (51%) patients had laparoscopic surgery and 66 (49%) patients underwent an open procedure. In univariate analysis, open surgery was not associated with an increased risk of postoperative complications (odds ratio: 1.4, 95% confidence interval: 0.6–2.9, $P = 0.433$). After adding the surgical approach to the multivariate regression model a high IL-6 remained independently associated with the occurrence of postoperative complications (adjusted odds ratio: 3.1, 95% confidence interval: 1.2–8.2; $P = 0.001$).

It is true that IL-6 is an inflammatory biomarker that is currently not routinely used in clinical practice. However, this should not preclude its use. Levels of IL-6 increase rapidly and peak after 24 hours, followed by levels of CRP peaking after 48 hours.⁵ As a result, IL-6 may facilitate earlier discrimination between patients with and without an increased risk of postoperative complications than CRP, as is shown by the results of our study. The analytic variance of IL-6 is equal to the analytic variance of high-sensitivity CRP measurements.⁶

We recognize that at this time an IL-6 assay is more expensive than a CRP assay. Nevertheless, if this facilitates early prevention or detection of postoperative complications the net health care costs are likely to be reduced.

Disclosure: Support was provided from institutional and departmental sources. The authors declare no conflicts of interest.

Thijs C. D. Rettig, MD
Lisa Verwijmeren, MD

Departments of Anesthesiology
 Intensive Care and Pain Medicine
 Nieuwegein, The Netherlands

Ewoudt M. W. Van de Garde, PharmD, PhD

Departments of Clinical Pharmacy
 St. Antonius Hospital
 Nieuwegein, The Netherlands

Djamilla Boerma, MD, PhD

Departments of Surgery
 St. Antonius Hospital
 Nieuwegein, The Netherlands

Peter G. Noordzij, MD, PhD

Departments of Anesthesiology
 Intensive Care and Pain Medicine
 Nieuwegein, The Netherlands
 p.noordzij@antoniusziekenhuis.nl

REFERENCES

1. Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFAS-study). *Ann Surg.* 2011;254:868–875.
2. Veenhof AA, Vlug MS, van der Pas MH, et al. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. *Ann Surg.* 2012;255: 216–221.
3. Veenhof AA, Sietses C, von Blomberg BM, et al. The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: a randomized trial. *Int J Colorectal Dis.* 2011;26:53–59.
4. Rettig TC, Verwijmeren L, Dijkstra IM, et al. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. *Ann Surg.* 2015 [Epub ahead of print]. Accessed September 4, 2016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26135695>.
5. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth.* 2000;85:109–117.
6. Karakas M, Baumert J, Greven S, et al. Reproducibility in serial C-reactive protein and interleukin-6 measurements in post-myocardial infarction patients: results from the AIRGENE study. *Clin Chem.* 2010;56:861–864.

Segment 4: a Key Point of ALPPS Procedure

To the Editor:

We read with interest the work of Clavien et al.¹ “Is partial-ALPPS safer than ALPPS? A single-center experience.” The authors conclude that when compared with patients who underwent complete partition, those who underwent 50% to 80% partition displayed similar liver hypertrophy kinetics that allowed for completion of the second stage, fewer severe complications after stage one procedure, and reduced operative mortality. They speculate that the partial liver partition approach—that is, associating liver partition and portal vein ligation for staged hepatectomy (p-ALPPS)—is a safer operation than traditional ALPPS.

The initial enthusiasm, generated by the work of Schnitzbauer et al² was followed by a general skepticism for the high morbidity rates ranging from 59% to 64% and a higher in-hospital mortality rates of 12 to 16%