Prognostic Utility of Postoperative C-reactive Protein for Posthepatectomy Liver Failure

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Hypothesis: C-reactive protein (CRP) is an acute-phase protein produced by the liver. We hypothesize that an early dampened CRP response after major liver resection is of prognostic importance in predicting post-hepatectomy liver failure (PHLF).

Design: Serum CRP levels were determined on postoperative days 1, 3, and 7 in patients undergoing liver resection (stratified into minor [≤2 segments], standard [3 or 4 segments], and extended [≥5 segments]). Correlations were made with indices of PHLF (hyperbilirubinemia, coagulopathy, ascites, and encephalopathy), multi-organ dysfunction syndrome, sepsis, and death.


Patients: One hundred thirty-eight individuals who underwent liver resection.

Main Outcome Measures: Sepsis, PHLF, and mortality.

Results: A total of 138 liver resections (39 minor, 51 standard, and 48 extended) were included. Median serum CRP levels on day 1 were significantly lower after extended liver resection (28 mg/L; range, 5-119 mg/L [to convert to nanomoles per liter, multiply by 9.524]) compared with standard resection (41 mg/L; range, 5-85 mg/L) and minor resection (51 mg/L; range, 8-203 mg/L; χ² = 19; P < .001). Similar differences were observed on day 3 (χ² = 27; P < .001). Postoperative day 1 CRP levels were significantly lower in patients developing PHLF (hyperbilirubinemia, P = .001; ascites, P < .001; coagulopathy, P = .002; and encephalopathy, P < .001) or multiorgan dysfunction syndrome (P = .009) or who died (P = .01). Day 1 serum CRP levels and extent of resection were independent predictors of PHLF in multivariate analysis.

Conclusion: The early dampened CRP response after major liver resection may reflect poor hepatic reserve that could have prognostic utility.


Liver resection remains the most effective therapy for patients with primary liver tumors and metastases from colorectal cancer. In many prospective and retrospective studies, liver resection has been shown to be a safe and effective therapy that prolongs survival. Five-year survival after surgical resection ranges from 20% to 51%, depending on preoperative selection criteria and the nature of the tumor. The promising survival rates and low postoperative mortality rates have pushed the limits of liver resection toward leaving smaller liver remnants to achieve potentially curative surgery. However, postoperative complications occur in 20% to 50% of patients, and mortality is often related to liver failure (1%-5%) or septic complications (3%-9%). It seems that poor outcomes after hepatic resection are often related to the ability of the remnant liver mass to cope with the physiologic and metabolic demands of the body. The critical liver mass, that is, the minimal functional liver mass needed for survival, is estimated to be 20% to 25% in patients with normal liver parenchyma, increasing to 40% in patients with abnormal parenchyma (cholestasis, fibrosis, cirrhosis, or steatosis). Exceeding the critical liver mass results in hepatic dysfunction and impaired regenerative capacity. A variety of preoperative selection criteria have been used to predict posthepatectomy liver failure (PHLF), including the prediction of residual liver volume using computed tomography volumetric analysis, indocyanine green excretion, and serum hyaluronic acid levels. Despite the availability and use of these tests, postoperative liver dysfunction and failure remain a problem in a subgroup of patients. However, the availability of an early postoperative prognosticator of PHLF may permit the timely introduc-

See Invited Critique at end of article

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tion of aggressive liver support to allow the liver to regenerate and prevent PHLF.

C-reactive protein (CRP) is a pleiotropic protein produced predominantly in the liver in response to interleukin 6 (IL-6) stimulus. C-reactive protein is believed to have a variety of functions: enhancement of phagocytosis through classical complement activation, increased expression of endothelial adhesion molecules, and up-regulation of pro-inflammatory (IL-8, tumor necrosis factor α, and plasminogen activator inhibitor 1) and anti-inflammatory (IL-10, interferon γ, and IL-1β) cytokines. Liver resection is associated with a significant increase in serum CRP concentration, even in patients with diseased livers. Given that CRP is produced by the liver, the aim of this study was to determine whether early postoperative serum CRP concentration reflects the functional capacity of the remnant liver and whether this measure has any prognostic utility in predicting poor outcome. We examined serial postoperative serum CRP concentration in patients undergoing minor to major liver resections and correlated this to indices of liver failure, multiorgan dysfunction syndrome (MODS), septic complications, and death.

**METHODS**

Local research ethics committee approval was obtained from the Leeds Teaching Hospitals National Health Service Trust (Leeds East), England. Adult patients admitted for elective liver resection surgery between January 1, 2002, and January 31, 2004, were considered for inclusion in the study. Patients with evidence of coexistent infection or inflammatory disease (acute or chronic), chronic organ failure, jaundice, or preexisting chronic liver disease (fibrosis or cirrhosis) and patients taking immunosuppressants or corticosteroids were excluded. Patients who had received chemotherapy within 3 months of elective liver surgery were also excluded.

Patients were divided into 3 groups corresponding to the extent of liver resection: minor, 2 segments or less or wedge resection; standard, 3 or 4 segments; and extended, 5 or more segments. Patients were operated on by 3 consultant liver surgeons (G.J.T., P.A.L., and K.R.P.) and were treated in accordance with a standardized departmental protocol.

**RESULTS**

The extent of liver resection was determined by preoperative radiologic investigations to assess the tumor burden in the liver, major vascular involvement, and extrahepatic disease using contrast-enhanced computed tomography of the chest, abdomen, and pelvis and magnetic resonance imaging of the liver. The number and size of the metastases were not used as selection criteria.

All the patients underwent surgery through a midline or transverse upper abdominal incision, and all the operations were performed under low central venous pressure, as previously described. Postoperative management included administration of 400 mL of salt-poor albumin with 1 mg of bumetanide daily for 5 days in addition to clotting factors to correct coagulopathy if the activated partial thromboplastin time exceeded 30 seconds (not routinely given). Liver function tests (serum total bilirubin, alkaline phosphatase, and alanine-1-transpeptidase [ALT]) were performed and coagulation (international normalized ratio [INR]) and CRP levels were measured preoperatively and on postoperative days 1, 3, and 7 in peripheral venous blood samples in all the patients. Levels of CRP were measured using an enzyme-linked immunosorbent assay (Dako, High Wycombe, England). The reference CRP value in serum is less than 10 mg/L (to convert to nanomoles per liter, multiply by 9.524).

**PRIMARY AND SECONDARY OUTCOMES**

Primary outcomes were the development of empirical markers of liver failure on postoperative day 7, including (1) persistent hyperbilirubinemia (serum bilirubin level >4.1 mg/dL [to convert to micromoles per liter, multiply by 17.104]), (2) coagulopathy (INR >2.5, despite early attempted correction with clotting factors), (3) abdominal ascites (drainage volumes >500 mL/d), and (4) encephalopathy with hyperbilirubinemia and exclusion of other acute confusional states. Secondary outcomes were the development of MODS (in accordance with American College of Chest Physicians criteria), or sepsis (includes sepsis syndrome and culture-proven infected abdominal collections), or in-hospital mortality.

**STATISTICAL ANALYSIS**

Results are expressed as medians (ranges). Comparison between the groups was performed using the Mann-Whitney test. The Pearson correlation coefficient was calculated when indicated for continuous data, and the Spearman coefficient was used for ordinal data. Binary logistic regression multivariate analysis was used to determine the predicted value of continuous and categorical variables. Significance was accepted at the P=.05 level. Statistical analysis was performed using a statistical software program (SPSS v5.0; SPSS Inc, Chicago, Illinois).

**PROCEDURES**

The most common indication for liver resection in all the groups was colorectal liver metastases; other indications included cholangiocarcinoma, hepatocellular carcinoma, esophageal and gastric metastases, and meta-

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**Table 1. Demographics of the Patient Groups and Indications for Surgical Resection**

<table>
<thead>
<tr>
<th>Indications for surgical resection, No. (%)</th>
<th>Minor Resection (n=39)</th>
<th>Standard Resection (n=51)</th>
<th>Extended Resection (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal liver metastases</td>
<td>32 (82)</td>
<td>47 (92)</td>
<td>38 (79)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>3 (8)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other (eg, neuroendocrine or esophageal metastases)</td>
<td>4 (10)</td>
<td>2 (4)</td>
<td>9 (19)</td>
</tr>
</tbody>
</table>

Abbreviation: ASA, American Society of Anesthesiologists.
static neuroendocrine tumors (Table 1). In addition, 9 patients underwent vascular resection or reconstruction (3 patients undergoing extended resections had portal vein resections, 1 had combined inferior vena cava and portal vein resection, 2 had inferior vena cava resection alone, and 3 had middle hepatic vein resections). Inflow occlusion (Pringle maneuver) was performed in 41.3% of all operations, with an overall median time of 20 minutes (range, 5-80 minutes). The duration of portal vein occlusion was similar in all 3 groups.

### PRIMARY AND SECONDARY OUTCOMES

Hyperbilirubinemia was present in 30 patients (21.7%), ascites in 11 (8.0%), coagulopathy in 10 (7.2%), and encephalopathy in 18 (13.0%). All 4 markers were significantly more common in patients undergoing extended resections compared with standard resections and the latter compared with minor resections \( (P < .001) \) (Table 2). The extent of resection was an independent predictor of PHLF in multivariate analysis (Table 3).

Overall mortality was 5.1%, MODS developed in 5.8% of patients, and septic complications occurred in 7.9%. Mortality and MODS were entirely confined to the extended resection group, although septic complications occurred in extended resections compared with standard resections and the latter compared with minor liver resections (Table 2). Overall mortality for all liver resections during this period was less than 2.1%.

### BIOCHEMICAL RESPONSE AFTER LIVER RESECTION

Serum CRP concentrations peaked on postoperative day 3 (median, 88.9 mg/L; range, 21-464 mg/L) and demonstrated a similar pattern of response as INRs (Figure 1). Levels of CRP correlated inversely with INRs on postoperative day 1 \( (r = -0.29; P = .002) \) and day 3 \( (r = -0.36;\)
$P < .001$) but not on day 7. There was no correlation with serum ALT concentrations.

Serum CRP concentrations on days 1 and 3 were significantly lower after an extended resection vs a standard resection and after a standard resection vs a minor resection (Figure 1A). An opposite pattern was observed with INRs, in which levels were higher after extended resection (Figure 1B). Serum ALT concentrations did not demonstrate any correlation with extent of liver resection.

Median serum ALT levels were significantly higher in patients who underwent a Pringle maneuver vs those who did not on postoperative day 1 (289 IU/L [range, 24-1235 IU/L] vs 163 IU/L [range, 26-855 IU/L]; $P < .001$) and day 3 (144 IU/L [range, 42-759 IU/L] vs 95 IU/L [range, 19-571 IU/L]; $P < .001$). There were no significant differences in day 7 ALT concentrations ($P = .37$) or either serial CRP ($P = .21$) or INR concentrations ($P = .42$) throughout the sampling period between the 2 groups.

**CORRELATION OF EARLY SERUM CRP CONCENTRATION AND INR WITH PHLF INDICES**

Serum CRP levels were significantly lower in patients who developed persistent hyperbilirubinemia ($P < .001$), ascites (day 1, $P < .001$; day 3, $P = .002$), encephalopathy ($P < .001$), and coagulopathy (day 1, $P = .002$; day 3, $P = .004$) (Figure 2). Serum INRs were conversely significantly elevated in patients who developed hyperbilirubinemia ($P < .001$), ascites ($P = .005$), and encephalopathy ($P < .001$), and the relationships remained significant even on days 3 and 7. The number of PHLF indices present in each patient correlated positively with postoperative day 1 INRs ($r = 0.50; P < .001$) and showed a strong inverse correlation with day 1 serum CRP concentrations ($r = -0.55; P < .001$) (Figure 3). Serum CRP concentration on postoperative day 1 was an independent predictor of PHLF in multivariate analysis, irrespective of extent of resection, age, American Society of Anesthesiologists score, or previous exposure to chemotherapy (Table 3). There were no significant demonstrable differences by postoperative day 7.

**SERUM CRP CONCENTRATION, MODS, SEPSIS, AND MORTALITY**

On postoperative day 1, serum CRP concentrations were significantly lower in patients who developed MODS (day 1, $P = .009$; day 3, $P = .05$) or septic complications (day 1, $P = .02$; day 3, $P = .21$) and in those who died (day 1, $P = .01$; day 3, $P = .04$) (Figure 4). For all the patients who developed MODS or sepsis and for those who died, day 1 CRP concentrations were less than 32 mg/L (sensitivity, 100%). Low serum CRP concentrations (<32 mg/L) were observed in 4 of 39 patients (10.2%) after minor resections (of which 1 [25.0%] developed hyperbilirubinemia and no secondary outcomes), 17 of 51 (33.3%) after standard resections (of which 6 [35.3%] developed primary outcomes and 2 [11.8%] secondary outcomes [sepsis]), and 31 of 48 (64.6%) after extended resections (of which 25 [80.6%] developed primary outcomes and 9 [29.0%] developed secondary outcomes [7 died]). Patients who underwent major liver resections (standard or extended resection) with postoperative day 1 serum CRP concentrations greater than 32 mg/L did not develop indices of liver failure or succumb to MODS, sepsis, or death (sensitivity, 100%; specificity, 100%). A serum CRP concentration less than 32 mg/L on postoperative day 1 was an independent predictor of PHLF (Table 3).

**CRP AND INR RESPONSES TO SEPSIS**

Patients who had major (standard and extended) liver resections were stratified into 2 groups based on a serum
CRP concentration of less than 32 mg/L on postoperative day 1 to examine the effect of sepsis on systemic CRP levels. All 11 patients who developed septic complications were among the 48 patients with a CRP level of 32 mg/L or less. Median serum CRP levels increased significantly by day 7 in patients who developed septic complications (27.6 mg/L; range, 17.2–32.0 mg/L) compared with those who did not (20.9 mg/L; range, 5–32 mg/L; \( P = .004 \)) (Figure 5). In the latter group, no significant change in CRP concentration was observed during the 7-day sampling period, whereas in patients who developed sepsis, a significant increase in CRP concentration was observed (\( P = .02 \), Wilcoxon signed rank test).

Serum INRs peaked on day 3 in both groups of patients; however, the pattern of response was similar in both groups at day 7 (Figure 6). Levels tended to be significantly higher in patients with sepsis on day 3 (\( P = .02 \)) and day 7 (\( P = .04 \)) (Figure 6).

**COMMENT**

Attempts to push the limits of liver resection to benefit more patients with primary and secondary liver tumors have been limited by the problem of PHLF. Several strategies to reduce PHLF have evolved during the past decade, including the use of computed tomographic volumetry, preoperative portal vein embolization, biliary drainage, and the liberal use of quantitative liver function tests such as indocyanine green excretion, all have been directed to identify patients who would develop PHLF. Despite these measures, PHLF remains a significant problem. Once developed, the management of PHLF is mainly supportive therapy, and outcomes are often dismal.

These results demonstrate an inverse correlation between the extent of liver resection and serum CRP concentrations early in the postoperative period. Low CRP levels (<32 g/dL) on postoperative day 1 and the extent of resection were independent predictors of PHLF in multivariate analysis. Although we did not directly measure liver remnant volume, it can be assumed that the more extended the resection, the smaller the remnant liver volume. It is estimated that, after an extended hepatectomy, the liver remnant forms only 15% to 25% of the total liver mass, increasing to 35% to 50% after a standard hepatectomy and more than 85% after minor liver resection. It would therefore be feasible to assume that CRP concentration reflects the synthetic capacity of the remnant liver, tested by the fact that CRP also correlated with indices of PHLF and inversely with INR.
The production of acute-phase proteins requires a pro-inflammatory cytokine as a mediator.\textsuperscript{13,14} Induction of CRP in hepatocytes is principally regulated at the transcriptional level by the cytokine IL-6, an effect that can be enhanced by IL-1β.\textsuperscript{13} Extrahepatic synthesis of CRP has also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes.\textsuperscript{16,17} The mechanisms regulating synthesis at these sites are unknown, and it is unlikely that they substantially affect plasma levels of CRP.

Interleukin 6 is a cytokine that has pro-inflammatory and anti-inflammatory properties and not only is important for inflammation and immunologic function but is required for acute-phase induction, which has been regarded as part of the attempt to maintain homeostasis.\textsuperscript{18} Furthermore, IL-6 is an important component of the early signal pathway leading to liver regeneration.\textsuperscript{19,20} Impaired hepatocyte proliferation and regeneration with subsequent liver failure after hepatectomy were observed in IL-6−/− knockout mice.\textsuperscript{21} Liver failure was prevented and the capacity of hepatocyte proliferation was restored by injecting IL-6 preoperatively.

Lan et al\textsuperscript{22} reported raised serum IL-6 and CRP responses after hepatectomy in patients with healthy (live related donor hepatectomy) and diseased (cirrhosis) livers, and a greater IL-6 stimulus is required as part of the regenerative process for an already diseased organ; however, the CRP responses were similar in both groups. An important functional role for CRP may be hypothesized, particularly because it has a variety of pro-inflammatory roles (activates the classical complement pathway; up-regulates the expression of adhesion molecules in endothelial cells; inhibits nitric oxide synthase expression; stimulates tumor necrosis factor α, IL-1, IL-8, and IL-18 release; and increases plasminogen activator inhibitor 1 expression and activity\textsuperscript{22,23}) and anti-inflammatory roles (induces expression of IL-1 receptor antagonist and increases release of the anti-inflammatory cytokine IL-10\textsuperscript{24} repressing synthesis of interferon γ).\textsuperscript{25} Interleukin 6 has been recognized as an important early signal for liver regeneration based on the IL-6−/− experiments\textsuperscript{21}; however, hyperstimulation with IL-6 administered to transgenic mice expressing soluble human IL-6 receptor (α) actually repressed cell cycle progression after hepatectomy, suggesting that IL-6 can inhibit liver growth after injury.\textsuperscript{25} It seems that an early IL-6 stimulus boosts cellular proliferation through the inhibition of apoptosis, but its prolonged effects may induce mitochondrial destabilization and potentiate liver injury.\textsuperscript{26}

All the patients who developed PHLF or sepsis or who died had serum CRP concentrations less than 32 mg/L on the first postoperative day. This association was independent of extent of resection on regression analysis, suggesting a potential prognostic role for CRP in predicting PHLF. To address whether this reflects impaired hepatic synthesis or is part of an adaptive physiologic response, we observed the serum CRP response to a septic insult in patients with low initial postoperative CRP concentrations. A septic complication even in these patients was associated with marked elevations in serum CRP concentrations, suggesting that their livers could generate substantial amounts of CRP in response to a “second insult.” This, together with the experimental data outlined herein,\textsuperscript{25,26} supports the adaptive physiologic response of the liver to maintain low CRP concentrations as part of the regenerative response.

The prognostic role of CRP is potentially useful for the timely intervention of liver support devices in patients likely to develop PHLF by decreasing hepatic toxic load in the immediate postoperative period to aid liver regeneration. The principles of the artificial devices, the molecular adsorbent recirculating system (MARS), are based on the filtration of albumin-bound toxins, and, although these have shown some benefits in patients with nonsurgical-related hepatic failure,\textsuperscript{27,28} the results after PHLF are less encouraging. Therapy with MARS seems to attenuate hyperbilirubinemia and hepatic encephalopathy after PHLF but has little survival benefit.\textsuperscript{29-32} Studies to date have been poorly controlled and consist of small cohorts; nevertheless, it is likely that, as concluded by a variety of MARS protagonists, too little is offered too late. A point of non-parenchymal recovery is reached after PHLF in which apoptosis supervenes with little chance of hepatic regeneration. Institution of support devices very early after extended hepatectomy in an identifiable risk group may improve survival, and this needs to be formally tested in randomized controlled studies.

In conclusion, serum CRP concentration after hepatectomy not only may reflect residual liver function but also may have an important metabolic role in regeneration. Its potential utility as an early index of PHLF and septic morbidity needs to be prospectively evaluated because this may provide a rationale for the instigation of targeted supportive therapy.

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Author Contributions: Study concept and design: Rahman, Toogood, Lodge, and Prasad. Acquisition of data: Rahman and Evans. Analysis and interpretation of data: Rahman, Evans, Toogood, Lodge, and Prasad. Drafting of the manuscript: Rahman, Evans, and Prasad. Critical revision of the manuscript for important intellectual content: Toogood, Lodge, and Prasad. Statistical analysis: Rahman. Administrative, technical, and material support: Rahman, Evans, Toogood, Lodge, and Prasad. Study supervision: Toogood, Lodge, and Prasad.

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REFERENCES

Maj or hepatic resections are often required for the treatment of primary and secondary hepatic malignancies. A key step in planning a major hepatectomy is predicting the risk of PHLF. It is generally accepted that a postoperative liver remnant volume of 25% or greater is sufficient to minimize the risk of PHLF in a healthy liver. However, this method is incapable of determining a subtle decrement in baseline hepatic function. This is a significant limitation in patients with cirrhosis or chemotherapy-induced steatohepatitis. To augment volumetric analysis, functional tests such as indocyanine green excretion are under investigation for their role as a predictor of PHLF. Because there is currently no effective means to bridge patients with PHLF to sufficient liver regeneration, the ideal predictor of PHLF should be a preoperative assessment. Rahman and colleagues propose the use of early postoperative serum CRP level to predict PHLF. As a result of the postoperative timing of this test, its clinical use will necessarily be limited. This criticism aside, their study nicely demonstrates a predictive role for postoperative day 1 CRP level based on its inverse correlation with PHLF indices. Although not emphasized, their data are also consistent with postoperative day 1 INRs, a predictor of PHLF (see Figure 1, compare A and B). In this regard, it is unclear how a CRP level adds any further predictive value over an early postoperative INR.

Estimation of postoperative residual function in the many patients undergoing hepatectomy in the setting of cirrhosis or after chemotherapy was not addressed in this study. It would be interesting to know whether preoperative CRP levels in these patients correlate with relative hepatic reserve and the development of PHLF, an interesting area of future investigation.

This well-executed study has identified yet another postoperative factor associated with PHLF. However, until a method of liver support is developed, the use of CRP for the determination of PHLF has limited clinical value.

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INVITED CRITIQUE

**Correction**

Missing Figure. In the article titled “Prognostic Utility of Postoperative C-reactive Protein for Posthepatectomy Liver Failure,” by Rahman et al, published in the March issue of the Archives (2008; 143[3]:247-253), Figure 3 was missing from the article on page 250. This article was corrected for error in data on February 28, 2008, prior to publication of the correction in print.

![Figure 3](image-url)

**Figure 3.** Scatterplot correlating the number of indices of posthepatectomy liver failure present in each patient and day 1 postoperative serum C-reactive protein (CRP) concentrations (to convert to nanomoles per liter, multiply by 9.524) ($r=-0.55; P<.001$, Spearman ρ correlation). Different symbols represent overlap of values. The dotted line indicates linear regression.