

# Early post-operative measurement of cytokine plasma levels combined with pre-operative bilirubin levels identify high-risk patients after liver resection

CHRISTOPH W. STREY<sup>1</sup>, ROSA MARIA MARQUEZ-PINILLA<sup>1</sup>, MACIEJ M. MARKIEWSKI<sup>2</sup>, BRITTA SIEGMUND<sup>1</sup>, ELSIE OPPERMANN<sup>1</sup>, JOHN D. LAMBRIS<sup>2</sup> and WOLF O. BECHSTEIN<sup>1</sup>

<sup>1</sup>Department of General and Vascular Surgery, Johann Wolfgang Goethe-University Frankfurt, Medical School, Frankfurt, Germany; <sup>2</sup>Department of Pathology and Laboratory Medicine, University of Pennsylvania, School of Medicine, Philadelphia, PA 19104, USA

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**Abstract.** Identification of patients at risk of a complicated course after liver resection is crucial for adapting post-operative care. In the present study, we investigated the diagnostic value of the plasma levels of various cytokines obtained immediately after surgery. IL-6, IL-10, IL-8, monokine induced by interferon- $\gamma$  (MIG), monocyte chemoattractant protein-1 (MCP-1) and interferon-inducible protein-10 (IP-10) concentrations were measured in 26 patients after liver resection using a cytometric bead assay and were correlated with liver function, resectate weight, surgery duration, ischemia/reperfusion, hospitalization time and occurrence of complications. Patients with post-surgical complications showed distinctive patterns of IL-6 and IL-8 as early as minutes to hours after surgery. In addition, although pre-operative bilirubin in most patients remained within the normal range, a cut-off of 1 mg/dl separated the patients into groups with different profiles of IL-6, IL-8, and MCP-1 secretion and different likelihoods of experiencing post-operative complications (bilirubin levels  $\geq 1.0$  vs.  $< 1.0$  mg/dl; IL-6 (4 h): 701 vs. 265; IL-8 (6 h): 262 vs. 97 pg/ml;  $p < 0.05$  for both). Extended hospitalization, related to delayed recovery, was correlated with increased IL-8 and MCP-1 immediately after surgery. In conclusion, on the basis of these observations, we suggest that early measurement of post-operative levels of MCP-1, IL-6, and IL-8 can be used to identify individuals at risk of post-operative complications immediately after liver surgery.

## Introduction

The frequency with which liver resections are carried out has increased in recent decades. This is a result of a growing number of patients with primary or metastatic liver tumors and of the inception of living-donor liver transplantation. Although the resection of liver parenchyma should, in theory, be a well-tolerated procedure given the high functional reserve and regenerative capabilities of this organ, in practice, partial hepatectomies are associated with complications that can lead to post-operative morbidity and mortality (1,2).

The highly diverse group of patients with varying comorbidity who undergo liver resection (LR) contributes to the difficulties inherent in identifying potential risk factors and predicting the patient's post-operative course. Another complicating factor for risk assessment is the estimation of the remnant liver volume depending on the extent of parenchymal resection (3,4). Early identification of individuals at high risk of developing LR-associated complications is a key determinant of appropriate and successful post-operative management (2). Several recent studies have pointed to cytokines released during surgery as potential predictors of the outcome of patients undergoing LR (5). It has generally been accepted that the brisk release of various pro-inflammatory cytokines is associated with worse prognosis and an increased risk of post-operative complications (5). However, some of these cytokines, including IL-6 and tumor necrosis factor (TNF)- $\alpha$  as well as other components of the innate immunity, have been found to be essential for regeneration of the liver parenchyma in various experimental models and liver diseases (6). Furthermore, we have recently shown that systemic anaphylatoxin release and neutrophil function is altered after LR, underlining the contribution of the complement system to the concert of proinflammatory mediators released in this context (7).

Recent studies have also indicated that IL-6 plays an important role in hepatoprotection in animal models of liver regeneration and acute liver failure (8). In addition, the surgical trauma associated with laparotomy and partial resection of the liver followed by liver regeneration is associated with a

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*Correspondence to:* Dr Christoph W. Strey, Department of General and Vascular Surgery, Johann Wolfgang Goethe-University Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany  
E-mail: strey@gmx.de

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risk of infection. Subsequent adaptive responses require the activation of inflammatory mechanisms that regulate tissue repair and protection against microbial spread (9-12).

This dual role of inflammation in the post-surgical recovery after LR poses challenges for developing effective therapeutic approaches to improve post-operative recovery by inhibiting inflammation. For example, the routine peri-operative administration of glucocorticosteroids has been thought to reduce hepatic injury (13); however, the effectiveness of this therapy remains controversial (14). Therefore, further studies identifying the risk indicators for liver surgery patients are highly desirable.

Although high levels of certain cytokines are known to be associated with an increased risk of post-operative complications after LR (5), it is unclear what pattern of secretion is an indicator of poor prognosis, given that many of these cytokines are required for liver regeneration and hepatoprotection (8). We have now performed a high-throughput analysis of the dynamics of secretion of various proinflammatory cytokines and chemokines in patients who have undergone hepatectomy and have correlated the levels of these mediators with clinical variables associated with prognosis and post-operative recovery.

Remarkably, we found that as early as minutes to hours after surgery, patients with a high probability of post-surgical complications could be identified on the basis of the combined patterns of IL-6 and IL-8 secretion. Furthermore, we discovered that although pre-operative levels of bilirubin in the majority of patients remained within the normal range, a cut-off level of 1 mg/dl could be used to separate liver resected patients into groups with different profiles of IL-6, IL-8, and MCP-1 secretion and different likelihoods of post-operative complications. In addition, an extended length of hospitalization, related to delayed recovery after surgery, was correlated with higher levels of IL-8 and MCP-1 immediately after surgery. Therefore, we suggest that early measurement of post-operative levels of MCP-1, IL-6, and IL-8 should be incorporated into the diagnostic algorithm for patients undergoing hepatectomy and that, in combination with the measurement of pre-operative levels of bilirubin (15), these values can be used to identify individuals at risk for post-surgical complications after LR.

## Materials and methods

**Patients.** All study procedures were approved by the Ethics Committee of the University Hospital of Frankfurt, and written informed consent was obtained from all patients. Twenty-six patients recruited to this study were admitted to the University Hospital of Frankfurt because of various conditions that required LR. Demographic data [age, sex, co-morbidity, body mass index (BMI)] and medical history, including laboratory values [total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and thromboplastin time (Quick)], for all individuals involved in the study were available to the investigators.

**Blood sampling.** Blood samples were collected from all patients into EDTA tubes containing Futhan (50 µg/ml) before surgery, as well as at 10 and 30 min and at 1, 2, 4, and

6 h after resection, and on post-operative days 1, 3, 4, and 7. Plasma was separated by centrifugation at 2000 x g for 15 min at 4°C and immediately stored in aliquots at 80°C.

**Cytometric bead assay.** Plasma levels of cytokines (IL-6, IL-10) and chemokines [IL-8; monocyte chemoattractant protein-1 (MCP-1); interferon-inducible protein-10 (IP-10); and monokine induced by interferon-γ (MIG)] were determined using the Cytometric Bead Array Human IL-6 Flex Set, the IL-10 Flex Set, and the Human Chemokine Kit I (Becton-Dickinson, San Diego, CA) according to the manufacturer's instructions. Details of the cytometric bead assay procedure have been previously described (16). In brief, a 1:1 mixture of diluted (1:200) plasma and capture beads was incubated for 2 h at room temperature in the dark, washed, and incubated with PE-conjugated detection antibodies for 1 h at room temperature in the dark. Complexes were evaluated by 2-color flow cytometric analysis using a FACScalibur flow cytometer (Becton-Dickinson Immunocytometric Systems, San Jose, CA).

Cytometric bead assay results were analyzed using the FCAP Array™ software (Becton-Dickinson). Plasma levels of cytokines and chemokines were evaluated and stratified according to pre-operative liver function (as determined by pre-operative total bilirubin levels), weight of the liver resectate, duration of surgery, ischemia/reperfusion (Pringle maneuver), and duration of post-operative hospitalization. The occurrence of post-operative complications, including surgical complications (bile duct leakage), organ dysfunction (heart failure, liver failure, post-operative ileus), infectious complications (pneumonia, urinary tract infections, wound infections), and post-operative hepatic function, were also analyzed.

Concentrations were expressed as means ± standard error (SE), and comparisons between groups were made using analysis of variance (ANOVA) for longitudinal measurements and the non-parametric Mann-Whitney U-test of significance or the unpaired Student's t-test. p-values <0.05 were considered statistically significant. All statistical analyses were performed using the StatView® software.

## Results

**Patients and surgeries.** We analyzed data for 26 patients (15 males and 11 females; mean age, 62.5±2.4 and 57.6±4.6 years, respectively) who were scheduled for LR for the following reasons: hepatic metastases of colorectal carcinoma (n=15); primary intrahepatic cholangiocarcinoma (n=6); primary hepatocellular carcinoma (n=2); and benign liver tumors (n=2), such as hemangiomas and adenomas. In two patients, an additional diagnosis of liver cirrhosis was established. The extent of the surgery was determined on the basis of the individual's indications, with 12 patients undergoing sectionectomies, which were termed minor resections (MinR), and 14 patients undergoing hemihepatectomies or extended resections, which were termed major resections (MajR). The age and gender distribution did not differ between the two LR groups (MajR vs. MinR: 63±2.2 vs. 57.5±4.4 years; Table I). The mean resectate weight was higher for patients with MajR (565±151 g) than for those with MinR (150±43 g, p<0.001). The Pringle maneuver (hepatic inflow occlusion), designed

Table I. Intra- and post-operative parameters.

	MinR mean $\pm$ SE	MajR mean $\pm$ SE	p-value
Age, years	57.5 $\pm$ 4.4	63.0 $\pm$ 2.2	NS
Gender (M/F), n	4/8	11/3	
Weight of resectate, g	150 $\pm$ 43	565 $\pm$ 151	<0.001
Duration of surgery until resection, min	88.5 $\pm$ 13.8	145.2 $\pm$ 12.9	<0.05
Length of hospital stay, days	11.5 $\pm$ 1.8	17.7 $\pm$ 2.8	<0.05
Patients undergoing Pringle maneuver, n	9	5	NS
Duration of Pringle maneuver, min	22 $\pm$ 7	26 $\pm$ 6	NS
Transfusions, number of erythrocyte concentrates given (n)	1 (2)	3 (2-4)	NS

MinR, segmentectomy (N=12); MajR, hemihepatectomy/extended resection (N=14); N, total number of subjects; n, number of observations; NS, not significant; SE, standard error.

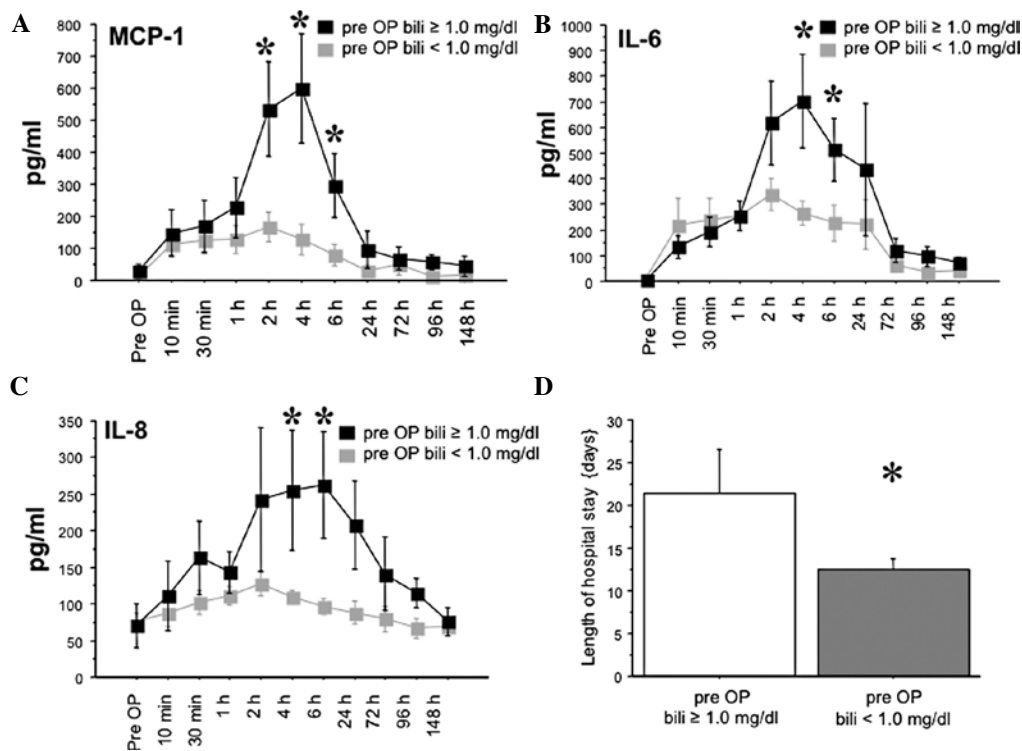


Figure 1. Pre-operative plasma bilirubin levels correlated with cytokine secretion after liver resection and the duration of post-operative hospitalization. Plasma levels of (A) MCP-1, (B) IL-6 and (C) IL-8 (pg/ml) after liver resection in patients with bilirubin levels  $\geq 1.0$  mg/dl (dark squares) or  $< 1.0$  mg/dl (light squares). (D) Duration of the hospital stay in the same groups of patients (Student's t-test, \* $p < 0.05$ ).

to prevent excessive blood loss during resection, was applied to 5 of 14 patients and 9 of 12 patients in the MajR and MinR groups, respectively. The average duration of the Pringle maneuver was  $24.2 \pm 2.8$  min and did not differ significantly between the two groups of patients.

*An elevated pre-operative plasma level of bilirubin affects cytokine secretion after liver resection.* Interestingly, we found that although the levels of bilirubin in the majority of patients were within the normal range, an arbitrarily selected cut-off of  $\geq 1.0$  mg/dl for the bilirubin concentration in plasma could

effectively divide the patient cohort into two different groups with significantly different profiles for MCP-1 (Fig. 1A), IL-6 (Fig. 1B), and IL-8 (Fig. 1C) secretion. Patients with bilirubin levels  $> 1.0$  mg/dl had significantly increased levels of these cytokines between 2-6 h after resection (Fig. 1A-C). In addition, the peaks of cytokine secretion occurred at 4-6 h after resection for all three cytokines in this group of patients. An increase in cytokine secretion above baseline levels was also observed in patients with bilirubin levels  $< 1.0$  mg/dl; however, the levels were lower, and the peaks of secretion were observed 2 h after surgery.

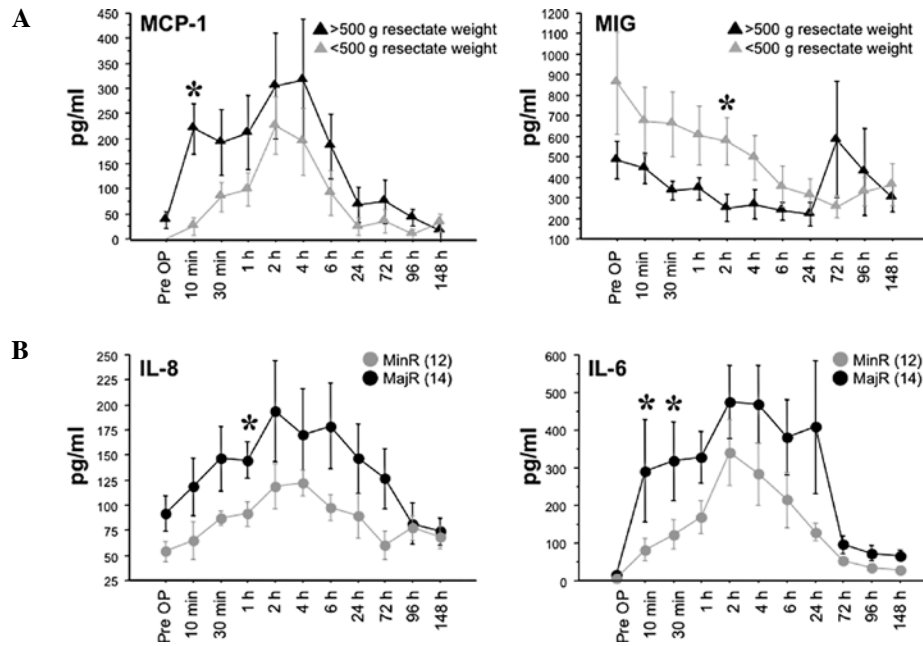


Figure 2. The extent of liver resection influences cytokine secretion. (A) Monocyte chemoattractant protein-1 (MCP-1) and monokine induced by interferon- $\gamma$  (MIG) plasma levels in patients classified into different groups according to the liver mass removed during resection (>500 g, dark triangles vs. < 500 g, gray triangles). (B) IL-6 and IL-8 levels in patients undergoing minor (MinR) (gray circles) or major (MajR) (dark circles) liver resection.

We hypothesized that this moderate early rise in cytokine secretion in patients with bilirubin levels <1.0 mg/dl reflects a physiological cytokine response that is required during the priming phase of liver regeneration and is needed to activate an immune response to protect against possible infection resulting from surgical trauma. The exacerbated and prolonged cytokine response that we observed in patients with initial bilirubin levels >1.0 mg/dl is a sign of a hyperactive inflammatory response that likely leads to post-operative complications.

Our hypothesis was confirmed by an analysis of the post-operative course in patients with different levels of bilirubin before surgery. We found that patients with bilirubin levels >1.0 mg/dl had a delayed recovery after surgery, as indicated by longer hospital stays (Fig. 1D). In addition,

similar differences in the patterns of IL-6 and IL-8 secretion were observed when the patient cohort was divided according to pre-operative plasma AST and AP levels, supporting the conclusion that pre-existing liver damage affects the cytokine expression after LR (data not shown).

*The extent of the liver resection primarily affects MCP-1 and MIG secretion, whereas the type of surgery affects IL-8 and IL-6 levels.* Removal of a large amount of liver parenchyma is associated with a higher risk of post-operative complication when compared to minor hepatectomies (18). In extreme situations, the remaining liver cannot sustain its metabolic, synthetic, and detoxifying functions, and this deficit in function leads to acute liver failure, with the typical clinical presentation developing 3-5 days after surgery.

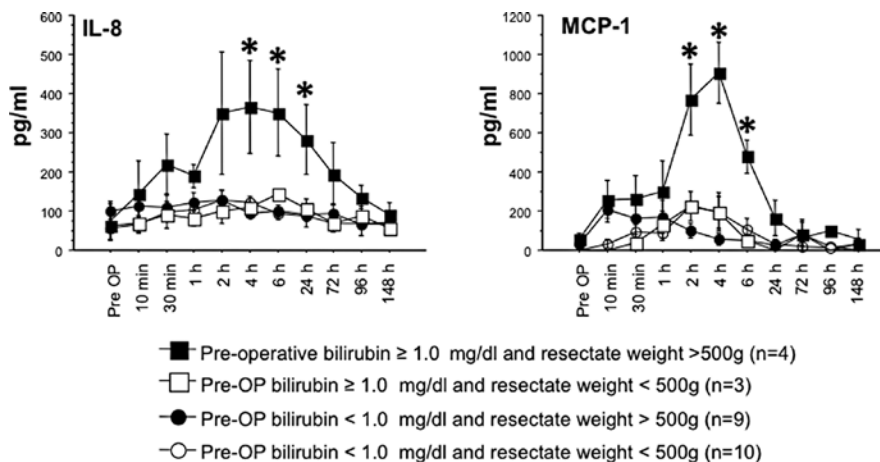


Figure 3. Elevated pre-operative plasma bilirubin levels in patients undergoing major liver resection (MajR) correlated with high post-operative levels of chemokines. Plasma levels of IL-8 and MCP-1 after resection in patients divided into four groups according to their pre-operative bilirubin levels (cut-off  $\geq$ 1.0 mg/dl) and the weight of liver removed (cut-off  $\geq$ 500 g).

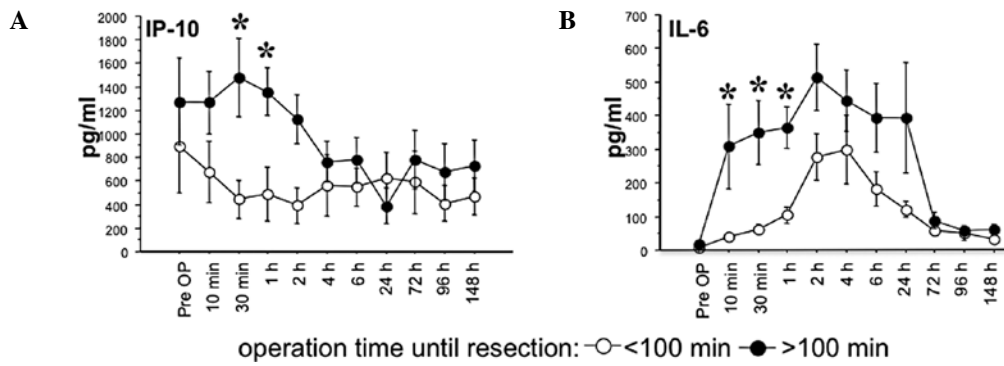


Figure 4. The length of the operation time until the end of the parenchymal resection phase has a significant influence on IP-10 and IL-6 levels after liver resection. Post-operative plasma levels of IP-10 (A) and IL-6 (B) according to the surgery time (<100 min, open circles; >100 min, filled circles) required to complete the resection of the liver parenchyma.

We therefore, looked for possible associations between the extent of LR and the cytokine profiles of plasma patients after surgery. This analysis revealed that those who underwent resection of >500 g of liver mass (n=13) had higher MCP-1 plasma values immediately after surgery than did those whose resections involved <500 g of liver mass (n=13,  $p<0.05$ ) (Fig. 2A). In addition, the level of MIG was lower 2 h after surgery in patients with a larger extent of surgery ( $p<0.05$ ) (Fig. 2A).

The type of liver surgery (MajR vs. MinR) affected the plasma levels of IL-8 and IL-6 (Fig. 2B), with higher concentrations being found in patients who had undergone more extensive surgery. However, despite the differences we observed in the concentrations of these cytokines, the patterns of secretions were similar for both groups (Fig. 2B). In addition, our combinatory analysis demonstrated that the pattern and levels of IL-8 secretion in patients who underwent extensive resection (>500 g of resected liver) and had higher pre-operative bilirubin levels (>1.0 mg/dl) were significantly

different from those in patients experiencing less extensive surgery (<500 g of resected liver) and lower pre-operative bilirubin levels (<1.0 mg/dl) (Fig. 3).

*The duration of surgery affects the IP-10 and IL-6 secretion.* Prolonged surgery is associated with more severe surgical trauma and frequently with longer periods of ischemia (19). Therefore, it is not surprising that these factors adversely affect post-operative recovery. In order to analyze the effect of the duration of surgery on cytokine release, we divided the patients in this study into two groups according to the time required to complete the resection phase. An extended duration of this phase of the operation, >100 min (n=15), was associated with a different profile and higher levels of post-operative plasma concentrations of IP-10 and IL-6 than in those seen for patients in which the LR had been completed within 100 min (n=11) (Fig. 4).

Given that the application of the Pringle maneuver during surgery is associated with temporary ischemia and with a

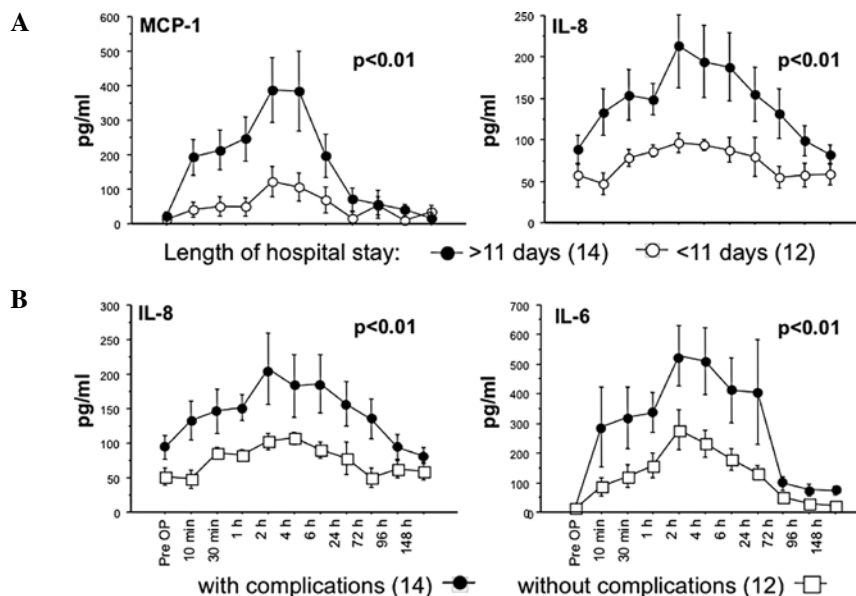


Figure 5. The duration of hospitalization and the presence of post-surgical complications affect plasma cytokine levels after liver resection. (A) Plasma levels of monocyte chemoattractant protein-1 (MCP-1) and IL-8 after liver resection in patients who were hospitalized >11 days (filled circles) vs. those who stayed in the hospital <11 days (open circles). (B) Plasma levels of IL-8 and IL-6 after liver resection in patients with various post-operative complications (filled squares) and those with an uncomplicated post-operative course (open circles). Statistical analysis was performed using ANOVA for longitudinal measurements.

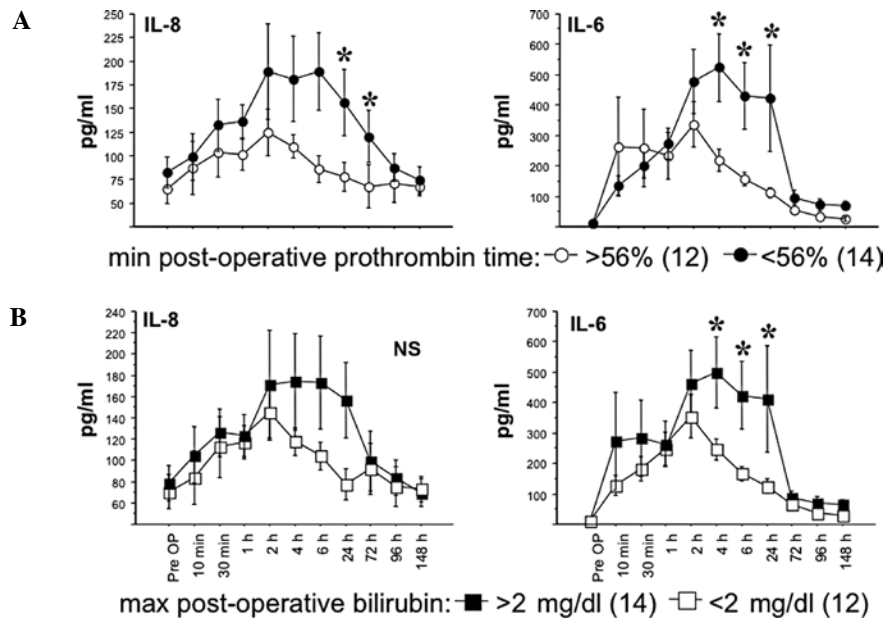


Figure 6. Liver function after resection correlated with the plasma levels of cytokines after surgery. (A) Plasma levels of IL-8 and IL-6 after liver resection in two groups of patients differentiated on the basis of liver function, as determined by minimal prothrombin time ( $Q < 56\%$ , filled circles;  $Q > 56\%$ , open circles). (B) Plasma levels of IL-8 and IL-6 in patients with post-operative bilirubin levels  $> 2$  mg/dl (filled squares) and those with post-operative bilirubin  $< 2$  mg/dl (open squares).

subsequent inflammatory response (20), we evaluated the influence of this surgical technique on cytokine secretion. However, we saw no significant differences in cytokine levels between those whose surgery had or had not involved the Pringle maneuver, presumably because of the relatively short duration of the arterial and portal occlusion in the patients in whom the Pringle maneuver was used (21).

*Delayed recovery and impaired liver function after resection are associated with alterations in the levels of MCP-1, IL-8, and IL-6.* The length of the hospitalization after surgery is directly related to the rapidity of recovery after surgical stress and the occurrence of post-surgical complications. Therefore, an extended post-operative hospitalization is a reliable indicator of delayed and difficult recovery after LR. We found that the plasma levels of MCP-1 and IL-8 were significantly higher in the patients who were hospitalized  $> 11$  days after surgery ( $n = 14$ ) than in those who left the hospital after a shorter period of time ( $n = 12$ ) (Fig. 5A). In addition, patients with various post-surgical complications such as a bile duct leakage ( $n = 3$ ), wound infection ( $n = 5$ ), intra-abdominal infection ( $n = 3$ ), liver failure ( $n = 3$ ), heart failure ( $n = 1$ ), urinary tract infection ( $n = 1$ ), or post-operative ileus ( $n = 2$ ), had higher levels of IL-6 and IL-8 at all the time points examined (Fig. 5B).

Importantly, higher levels of IL-8 and IL-6 were also observed in individuals with impaired liver function after surgery, as demonstrated by a prolonged prothrombin time (Fig. 6A). Also, in patients with post-operatively elevated bilirubin  $> 2$  mg/dl, the increase in plasma IL-6 was significantly more pronounced (Fig. 6B).

## Discussion

The early identification of the patients who are at risk of developing complications after LR is essential to adequately

modify their post-operative management. Although cytokine profiles have previously been proposed as prognostic factors in patients after LR (5) and other abdominal surgeries (22,23), in most of the relevant studies, the levels of various cytokines were evaluated days after surgery, when signs of the deterioration of liver function could be noted on the basis of the clinical evaluation. Therefore, these analyses offered only little improvement in the diagnostic process when compared to standard procedures.

We have now demonstrated that alterations in the secretion of several cytokines just minutes or hours after LR can contribute to the prediction of post-operative outcome. Compared to the application of the '50-50 criteria' on days 3 and 5 by measuring serum bilirubin and prothrombin time (2), patients at risk for complications will be identified earlier. Our results indicate that high levels of MCP-1, IL-6, and IL-8 observed shortly after surgery are directly correlated with a worse post-operative outcome or with other predictors of delayed post-operative recovery in patients undergoing LR. Importantly, we found that although IL-6 has been shown to participate in liver regeneration and hepatoprotection after partial hepatectomy (24,25), a brisk and early induction of this cytokine is clearly correlated with a worse post-operative outcome and impaired liver function after surgery. This observation underscores the importance of the kinetics and amount of IL-6 secretion in predicting the final outcome of the resection.

It is possible that moderate IL-6 induction is associated with beneficial pro-regenerative and hepatoprotective effects, whereas a sudden release of large quantities of this cytokine leads to dysregulation of the post-operative inflammatory response and significantly worsens the prognosis.

This dual role of inflammatory mediators in patient recovery after liver surgery, is well illustrated by the attempts to modulate post-operative inflammation through the pre-

operative application of steroids. Such therapy has resulted in a shorter post-operative hospital stay and in reduced bilirubin and TNF- $\alpha$  levels; however, neither a shortened convalescence time nor lower post-operative complication rates could be achieved (13,26).

Non-specific immunosuppression induced by steroids does not seem to alter the post-operative course to a clinically significant extent and is apparently associated with adverse effects. Moreover, the untargeted suppression of proinflammatory mediators, including IL-6, can result in an impaired regeneration of the liver and a higher level of liver tissue damage after surgery. These harmful effects of inhibiting the inflammatory response after LR have been demonstrated in a rat model of liver transplantation in which the administration of dexamethasone impaired liver regeneration (14).

However, modulation of inflammation might be a promising approach after LR, if this therapy could be applied to patients at high risk of developing a dysregulated hyperinflammatory response. Our results suggest that early monitoring of plasma levels of proinflammatory mediators, such as cytokines, could prove to be a strategy for identifying those patients who would benefit from anti-inflammatory drugs.

It is interesting that although most of the patients in our study population entered their liver surgery with physiologic bilirubin values, stratification of these patients according to their pre-operative bilirubin levels revealed an association between this parameter and the post-operative recovery and cytokine response. In particular, patients with bilirubin levels  $\geq 1.0$  mg/dl who underwent resection of  $>500$  g of liver tissue showed a pronounced post-operative inflammatory response. This observation is consistent with previous reports (18) and suggests that patients with even mildly impaired liver function are at risk for a complicated post-operative course when a large portion of the liver is removed. Pre-operative chemotherapy, can significantly influence the regenerative and compensatory capacity of the remaining liver parenchyma (17). This impairment in liver regeneration is associated with a delay in post-operative recovery after resection.

Conflicting results have been published concerning the inflammatory effect of hepatic inflow occlusion (Pringle maneuver) during liver surgery. The detrimental effect of ischemia and reperfusion on hepatocytes by CXC chemokine-mediated signaling has been described after 90 min of ischemia in mice (27). Some reports also found a proinflammatory effect during human liver surgery (21), while others stand in line with our observation indicating no significant impact of this maneuver on the pattern of cytokine secretion (28). These differences concerning the effect of the Pringle maneuver might in part be due to the duration of the hepatic inflow occlusion, which was short in our patients (22-25 min).

In conclusion, our results suggest that an evaluation of the plasma levels of various cytokines immediately after LR, combined with the routine evaluation of biochemical parameters of liver function, should become part of the diagnostic algorithm for patients undergoing partial hepatectomy. This approach has the potential to identify those patients who are at risk of post-operative complications within minutes or hours after surgery. Such early identification of individuals vulnerable to complicated post-operative recovery will lead to an improvement in the outcome after LR, because the

appropriate therapeutic measures can be carried out in time to prevent the deterioration of the patient's clinical condition.

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