

Low Postoperative Platelet Count is Associated with Higher Morbidity after Liver Surgery for Colorectal Metastase

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Abstract

Objective: Platelets play an important role in liver regeneration. One major problem after liver surgery represents the impaired postoperative liver function and delayed recovery.

The aim of this study was to evaluate the association of platelet counts to liver regeneration and postoperative outcome after liver surgery for colorectal metastases.

Methods: This study included 84 patients without chronic liver disease (such as viral hepatitis or liver cirrhosis) who received partial liver resection between July 2007 and July 2012 for colorectal liver metastases in our hospital. 65% received preoperative chemotherapy. All patients presented with normal liver function before surgery. Platelet counts were obtained between day -1 and day 12 to surgery and correlated with postoperative morbidity and mortality. Comparative analysis between patients with platelet counts $\leq 100/\text{nl}$ and $>100/\text{nl}$ one day after liver surgery was performed in regard to postoperative outcome and liver regeneration.

Results: Postoperative low platelet counts are associated with significant higher morbidity ($p=0.003$) and need of re-operation ($p=0.004$). Furthermore, thrombocytopenic patients showed impaired liver function with significantly higher bilirubin levels ($p=0.001$; $p=0.005$) and lower prothrombin time ($p=0.015$; 0.006) between day 1 and day 7.

Conclusion: Postoperative low platelet counts are associated with higher morbidity after liver surgery. Low platelet counts lead to impaired liver function with delayed recovery after liver surgery.

Keywords: Platelet counts; Liver surgery; Liver regeneration; Colorectal liver metastases; Liver failure

Introduction

Colorectal cancer is one of the most common malignant diseases [1]. Fifteen to twenty-five percent of patients with colon carcinoma show liver metastases at the time of diagnosis [2]. Furthermore, the same number of patients develops metachronous liver metastases. Development of multimodal strategies combining chemotherapy, targeted therapies (e.g. AB, SMI) and surgery lead to wider curative therapeutic options for liver metastases [3-7]. As a consequence, surgery of liver metastases from colorectal cancer became standard therapy. Nowadays colorectal liver metastases are the leading indication for liver surgery in the western world. One major problem in liver surgery is the postoperative liver failure. It is well known that chemotherapy can lead to liver damage with impaired regenerative capacity [8,9].

Platelets are known to play an important role in thrombosis and haemostasis. In recent years, extra- haemostatic functions of platelets were discovered. A new spotlight was put on the role of platelets in liver inflammation and liver regeneration [10,11]. It was shown that platelets play a pivotal role in liver regeneration. Lesurtel and colleagues showed that platelets as well as platelet-derived serotonin are involved in liver regeneration [12,13]. Those findings might be of central interest in surgery, enabling more extended liver resections by minimizing the risk of postoperative liver failure [13]. Various animal experiments in pigs, mice and rats confirmed the promotive effect of platelets after hepatectomy [14]. Delayed liver function after liver surgery for colorectal metastases in non-cirrhotic patients with postoperative low platelet counts has been described [15].

In this study, analyses of the association of platelet counts with the postoperative outcome after liver surgery was performed. Only patients

operated for liver metastasis of colorectal carcinoma were included in this analysis. Patients with liver cirrhosis and /or viral hepatitis were excluded from this analysis. First, patients were compared in regard to postoperative morbidity, mortality and need of re-operation and platelet counts were analysed. Second, patients were separated into two groups: group 1 included patients with platelet counts $\leq 100/\text{nl}$ and group 2 consists of patients with platelet counts $>100/\text{nl}$ one day after partial liver resection. Both groups were compared in regard to postoperative morbidity and mortality and liver function.

Methods

Study population

All patients undergoing liver resection for colorectal liver metastases between July 2007 and July 2012 in a single institution were prospectively recorded in an electronic database and analysed. Patients with pre-existing liver disease such as viral hepatitis or liver cirrhosis were excluded as were patients with simultaneous major visceral operations such as colorectal resections. Therefore a highly

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selected cohort was generated to minimize confounding influences on platelet numbers and outcome. Patient characteristics, pre- and postoperative treatment, laboratory values, operative procedures, intra- and perioperative data, complications, hospital stay, etc. were prospectively recorded in the database.

For preoperative imaging and surgical planning, at least one computed scan or MRI was performed.

Laboratory values

Platelet counts in patients were obtained the day before surgery (d-1), the day of surgery (d0) and 1 (d1), 3 (d3), 7 (d7) and 12 (d12) days after surgery. Serum concentrations of bilirubin, GGT, ALT, AST, haemoglobin and prothrombin time on d0, d1, d3, d7, d12 were obtained from patients.

Comparative analysis and outcome parameters

A comparison of patients with or without morbidity and mortality in regard of platelet count was performed. Patients were then divided into two groups: comparative analysis between patients with platelet numbers $\leq 100/\text{nl}$ (group 1) and $>100/\text{nl}$ (group 2) at d1 in regard to postoperative mortality, morbidity and need of re-operation and liver function was performed. Liver function and liver damage was monitored by liver-specific laboratory tests (bilirubin, AST, ALT, GGT, prothrombin time). The cut off at 100 platelets /nl was chosen as it was already chosen for comparative analyses by other authors before [15].

Postoperative course of platelet numbers

To clarify whether the absolute number of platelets or the increase and decrease of platelet counts is associated with the postoperative outcome, analyses of platelet numbers on d-1, d0, d1, d3 and d7 as well as the increase or decline between certain time points were performed in regard to postoperative liver failure, morbidity, mortality and need of re-operation. Liver failure was defined as bilirubin $>50 \mu\text{mol/l}$ and prothrombin time $<50\%$ [16].

Statistical Analysis

Statistical analysis was performed with R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics of quantitative data are given by median (range), due to deviations from the normal distribution. Accordingly, absolute and relative frequencies are presented for qualitative data. Group comparisons are performed by Mann-Whitney-U tests and Fishers exact tests on two-sided, explorative 5% significance levels.

Results

Patients' characteristics

84 patients who received liver surgery for colorectal liver metastases were included in the analysis. Median age of the cohort was 68 years (range 35-84). 36% received major hepatic resections while 64% received minor hepatic resections. The overall morbidity of this cohort was 23.8%, the overall mortality 2.4%. Detailed information is given in Table 1.

Comparison of platelet counts in patients with or without morbidity and mortality

The median platelet count was generally lower in patients with postoperative complications, the need of re-operation or in patients who died after the operation. As a matter of fact, groups (patients

Number of patients	N:84	
Age (years)	Median	68
	Range	35-84
Gender	Male	54 (64%)
	Female	30 (36%)
ASA Score	I:	0
	II:	62 (74%)
	III:	22 (26%)
	IV:	0
	V :	0
Pre-treatment	Yes	58 (69 %)
	No	26 (31 %)
Chemotherapy	Yes	55 (65%)
	No	29 (35%)
TACE	Yes	5 (6%)
	No	79 (94%)
RFA	Yes	9 (11%)
	No	75 (89%)
Preceding Operation	Yes	15 (18%)
	No	69 (82 %)
Liver resections performed	Right hemihepatectomy	19 (23%)
	Extended right hemihepatectomy	7 (8%)
	Left hemihepatectomy	3 (4%)
	Extended left	1 (1%)
	Anatomical resections:	20 (24%)
	Atypical resections:	34 (40%)
Technical devices	CUSA:	3 (4%)
	Electrocautery:	10 (12%)
	Stapler:	48 (57%)
	HABIB:	7 (8%)
	Waterjet:	16 (19%)

Table 1: Patients' characteristics

ASA: American Society of Anesthesiologists, TACE: transarterial chemoembolization, RFA: radiofrequency ablation, CUSA: cavitron ultrasonic surgical aspirator (CUSA, Cavitron, Inc. Stanford, Conn., USA), HABIB : bipolar resection device (HABIB, Unomed, Switzerland).

with morbidity vs. patients without morbidity) differ in regard to patient numbers. Even though platelet counts show wide ranges, the trend was throughout observable. Indeed, the differences between platelet counts are statistically significant in regard to morbidity at d0 ($p=0.006$), d1 ($p=0.003$) and d7 ($p=0.043$) and the need of re-operation at d0 ($p=0.011$), d1 ($p=0.004$), d3 ($p=0.024$) and d12 ($p=0.017$). The corresponding platelet curves are illustrated in Figure 1a and b.

Comparative analyses between patients showing platelet numbers $\leq 100/\text{nl}$ (group 1) and platelet numbers $>100/\text{nl}$ (group 2) one day after liver surgery

No statistically significant difference in the patients' characteristics shown in Table 1 was observed between these two groups. Especially there was no difference between the proportions of major or minor resections between these two groups.

Group 1 (platelets $\leq 100/\text{nl}$; $n=12$) showed a statistically significant higher morbidity rate (67%) than group 2 ($>100/\text{nl}$; $n=72$) (17%) ($p=0.003$) and a higher rate of re-operations ($p=0.004$) (Table 2).

Analysis of postoperative complications revealed that statistically significant more surgical complications occurred in thrombocytopenic patients (group 1) compared to group 2 ($p<0.001$) while no statistically significant difference was observed in regard to non-surgical complications ($p=0.136$). A detailed list of complications is given in Table 2.

Serum bilirubin levels and prothrombin time to evaluate liver function, as well as analyses of liver enzymes and haematological measures were performed in a comparative analysis.

	Overall (n:84)	Group 1 (platelets ≤ 100 / nl) (n: 12)	Group 2 (platelets >100 / nl) (n:72)	p-value
Mortality	2 (2.4%)	0	2 (3%)	1
Liver failure	0	0	0	
Re-operation	5 (5.9%)	4 (33%)	1 (1%)	0.004
Morbidity	20 (23.8%)	8 (67%)	12 (17%)	0.003
Surgical complications	16 (19%)	8 (66.7%)	8 (11.1%)	0
Abdominal abscess	2 (2.5%)	2(17%)	0	0
Wound dehiscence	1 (1.2%)	1 (8%)	0	0.004
Others	4 (4.9%)	2 (17%)	2 (2.8%)	0.011
Bilioma	1 (1.2%)	1 (8%)	0	0.004
Wound infection	4 (4.9%)	2 (17%)	2 (2.8%)	0.011
Perforation of the gut	1 (1.2%)	1 (8%)	0	0.004
Non-Surgical Complications	9 (11%)	3 (25%)	6 (8.3%)	0.136
Pulmonary	1 (1.2%)	1 (8%)	0	0.004
Sepsis	1 (1.2%)	1 (8%)	0	0.004
Others	4 (4.9%)	2 (17%)	2 (2.8%)	0.011

Table 2: Comparative analyses between patients showing platelet number of ≤ 100/nl or > 100/nl on the first postoperative day after liver surgery. Only complications with statistically significant differences between both groups are listed in detail.

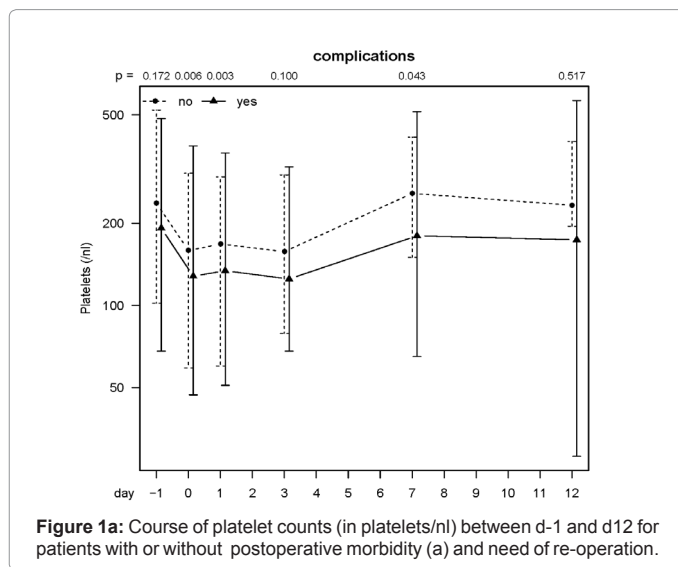


Figure 1a: Course of platelet counts (in platelets/nl) between d-1 and d12 for patients with or without postoperative morbidity (a) and need of re-operation.

Group 1 showed statistically significant higher serum bilirubin levels and reduced prothrombin time between d0 and d12, reflecting liver function (Figures 2a and 2b). Differently, the levels of haemoglobin, transaminases (AST and ALT) as well as the course of GGT were comparable in both groups between d-1 and d12 (Figure 2c-f). Therefore, blood loss, measured by the haemoglobin levels, and the extend of cellular damage to the liver, indicated by the transaminases, were comparable in both groups.

The delayed recovery of the liver function and the higher rate of postoperative complications were further reflected in the difference of postoperative ICU stay. There was a statistically significant difference in the ICU stay between the two groups due to the higher complication rate and number of reoperations: Patients with platelet numbers <100/nl showed a statistically significant higher ICU stay (median 3 days; range 1-37) compared to patient with platelet numbers >100/nl (median 1 day; range 0-37) one day after operation (p=0.002). However, there

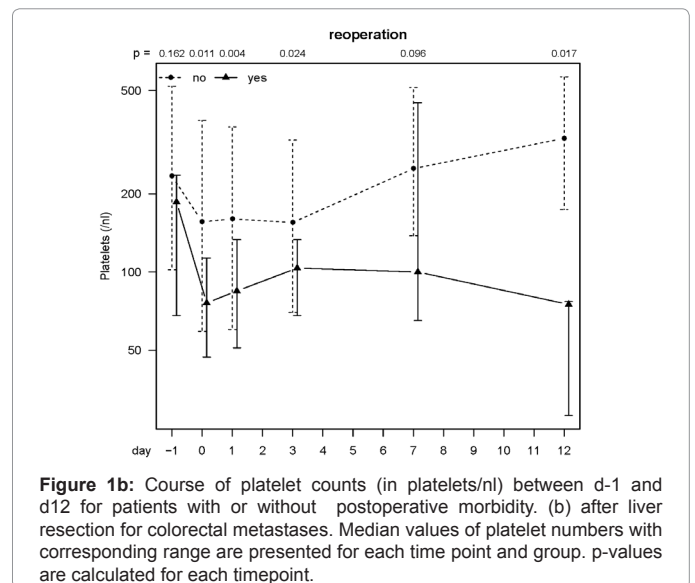


Figure 1b: Course of platelet counts (in platelets/nl) between d-1 and d12 for patients with or without postoperative morbidity. (b) after liver resection for colorectal metastases. Median values of platelet numbers with corresponding range are presented for each time point and group. p-values are calculated for each timepoint.

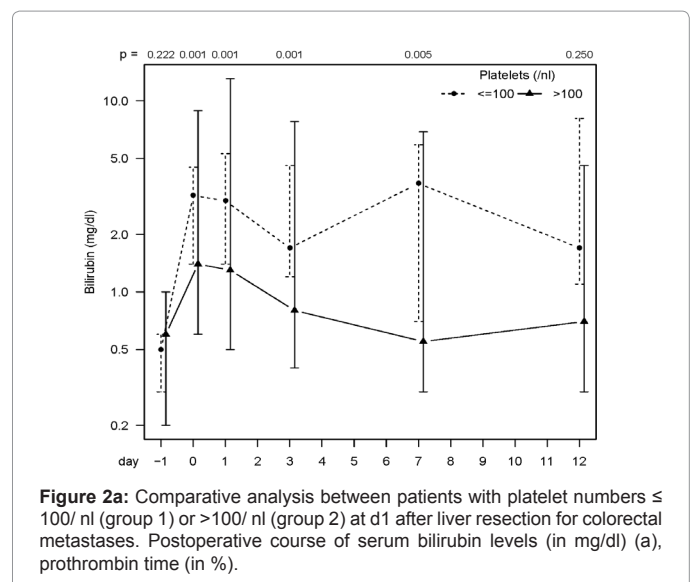


Figure 2a: Comparative analysis between patients with platelet numbers ≤ 100/ nl (group 1) or >100/ nl (group 2) at d1 after liver resection for colorectal metastases. Postoperative course of serum bilirubin levels (in mg/dl) (a), prothrombin time (in %).

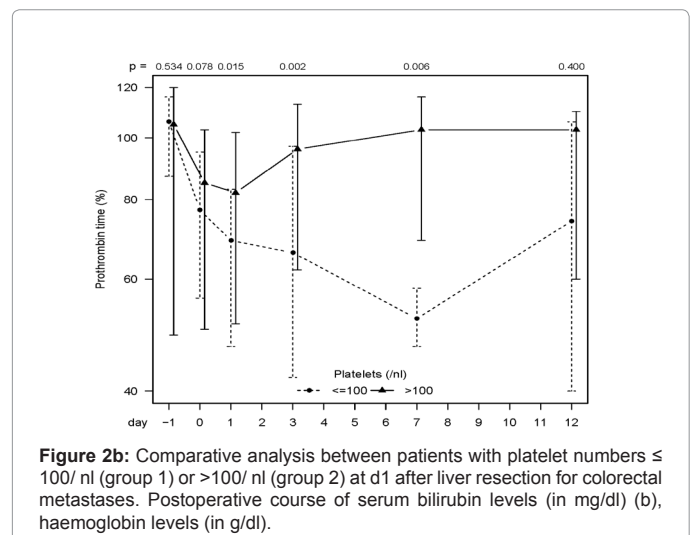


Figure 2b: Comparative analysis between patients with platelet numbers ≤ 100/ nl (group 1) or >100/ nl (group 2) at d1 after liver resection for colorectal metastases. Postoperative course of serum bilirubin levels (in mg/dl) (b), haemoglobin levels (in g/dl).

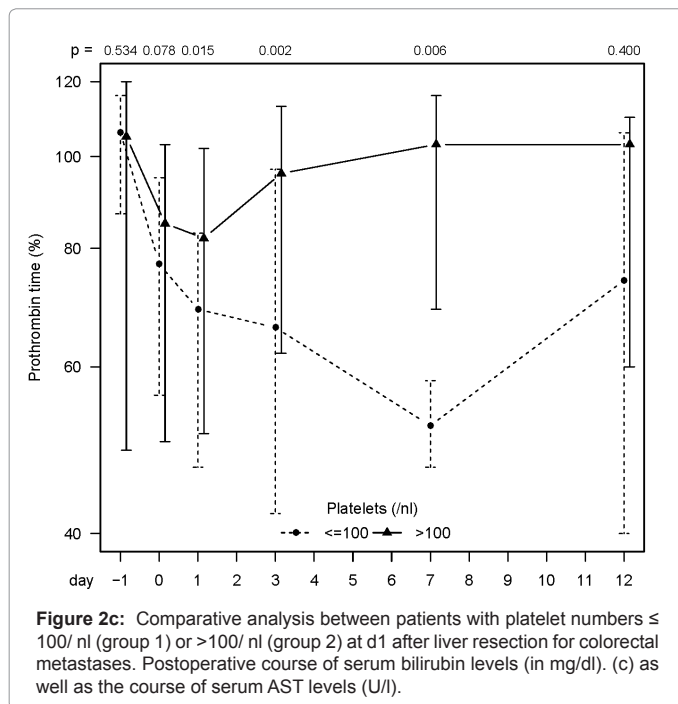


Figure 2c: Comparative analysis between patients with platelet numbers ≤ 100 /nl (group 1) or >100 /nl (group 2) at d1 after liver resection for colorectal metastases. Postoperative course of serum bilirubin levels (in mg/dl). (c) as well as the course of serum AST levels (U/l).

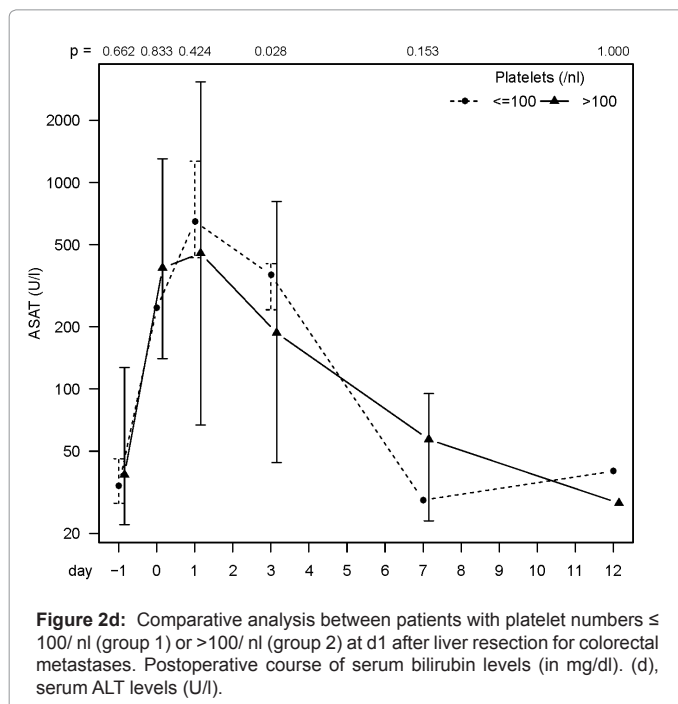


Figure 2d: Comparative analysis between patients with platelet numbers ≤ 100 /nl (group 1) or >100 /nl (group 2) at d1 after liver resection for colorectal metastases. Postoperative course of serum bilirubin levels (in mg/dl). (d), serum ALT levels (U/l).

was no statistically significant difference regarding days of mechanical ventilation on IUC ($p=0.214$).

Postoperative outcome after liver surgery is associated with postoperative platelet counts, but not with increase or decline of platelet numbers after liver surgery

To test whether the decline or increase of platelet counts is associated with postoperative liver regeneration, the median increase of platelets between d0 and d1, d0 and d3, d0 and 7 as well as the

decline between d-1 and d0 was calculated and compared in regard to postoperative morbidity, mortality and liver function. There was no statistically significant difference between patients presenting with postoperative liver failure, morbidity or mortality in regard to the decline or increase of platelet numbers (data not shown).

Therefore the absolute number of platelets is pivotal and not the change of the platelet count as long as it stays in the 'normal range'

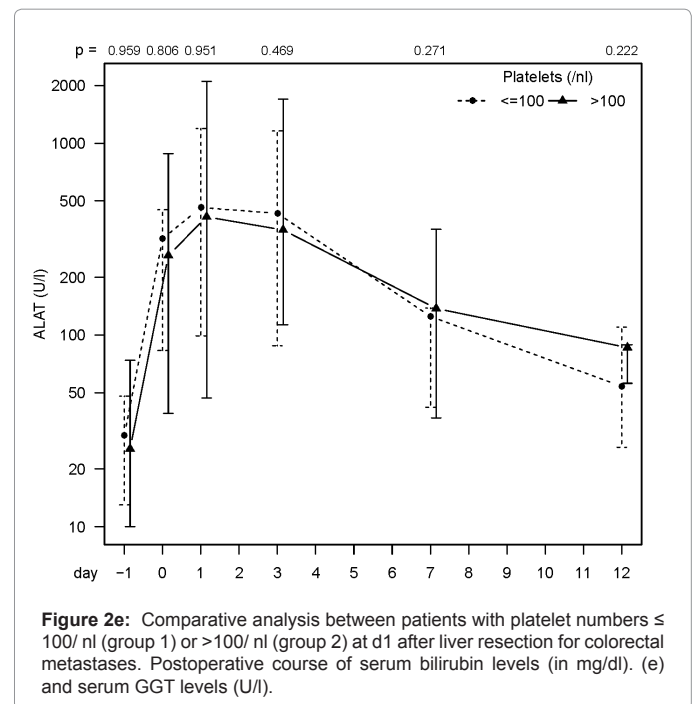


Figure 2e: Comparative analysis between patients with platelet numbers ≤ 100 /nl (group 1) or >100 /nl (group 2) at d1 after liver resection for colorectal metastases. Postoperative course of serum bilirubin levels (in mg/dl). (e) and serum GGT levels (U/l).

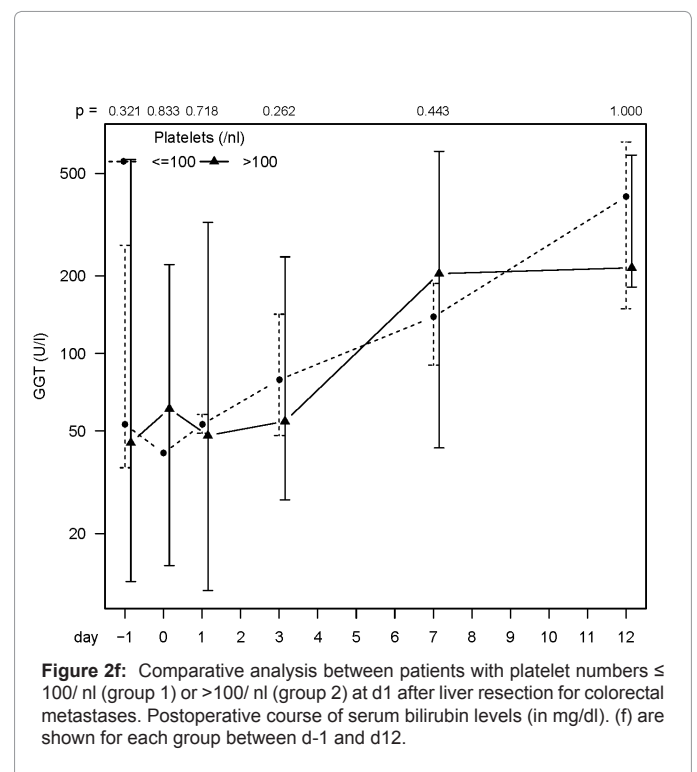


Figure 2f: Comparative analysis between patients with platelet numbers ≤ 100 /nl (group 1) or >100 /nl (group 2) at d1 after liver resection for colorectal metastases. Postoperative course of serum bilirubin levels (in mg/dl). (f) are shown for each group between d-1 and d12.

Discussion

Platelets play an important role in liver regeneration [10,11,13,14]. The liver-regenerative effect has been shown by several in-vitro experiments and animal models [11,14,17-19]. This has been confirmed by several animal studies [11,14,20-22]. The results of this study confirm that low platelet counts are associated with increased postoperative morbidity and need of operative revision after partial liver resections in humans. But is the platelet count essential for postoperative liver regeneration? Patients with postoperative low platelet counts presented with impaired liver function and delayed liver recovery, shown by higher bilirubin levels and lower prothrombin time between d1 and d7, compared to patients with normal platelet counts. Those findings go in line with Alkozai et al. [15]. Differently to Alkozai et al. [15], in this study, no significant difference in the postoperative course of serum AST, ALT and GGT levels between both groups was observed, even though the percentage of major hepatectomies is comparable in both studies. However, a limitation of this study is - as a matter of fact - that patient numbers in the comparative analysis between patients with high and low platelets numbers vary widely.

However in this study an analysis of a highly selected cohort that reflects the typical patients undergoing liver surgery for colorectal liver metastases without accompanying liver diseases or simultaneous major visceral surgery was evaluated. Most patients are in good clinical condition reflected in the ASA score (74% ASA II) and received pre-treatment in 68% including 65% chemotherapy. Therefore confounding influences on platelet numbers were minimized. Patients who receive surgery for colorectal liver metastases are of special interest since colorectal liver metastases are the leading indication for liver surgery in western countries. In those cases, liver surgery is mostly part of a multimodal therapeutic approach that combines neoadjuvant chemotherapy with/without antibodies such as anti- Vascular Endothelial Growth Factor (VEGF) antibodies as bevacizumab and surgical resection [23,24]. In addition, interventional radiologic tools like portal vein embolisation to induce hypertrophy of the future liver remnant prior to liver resection can be part of the multimodal strategy [25]. Advantages of neoadjuvant chemotherapy is cancer downstaging as well as a prolonged progression free survival [26,27]. On the other side, it has been described that chemotherapy can cause liver damage leading to impaired liver function and/or liver regeneration: 5-floururacil/leucovorin is linked to hepatic steatosis with postoperative increased infection rates. The chemotherapy-associated steatohepatitis, also known as CASH, is strongly associated with irinotecan with poorer liver regeneration and the Sinusoidal Obstruction Syndrome (SOS) is related to oxaliplatin [8,9,28,29]. Consequent, patients regularly present with risk for delayed liver recovery.

The present study showed that the absolute platelet counts are important for the postoperative outcome and the liver function. Decline or increase of platelet numbers did not influence the postoperative outcome when staying in the critical range.

Though the detailed mechanism is unclear, liver regeneration is mediated by platelets and platelet-derived serotonin [12]. Platelets contain many growth factors as Platelet Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), HGF, IGF, EGF and TGF β and some cytokines [17,19,30]. Due to those growth factors, platelets play a role in stimulation and acceleration of hepatocyte proliferation resulting in improved liver regeneration [11,18,20,31,32]. Mobilisation and increase of platelet numbers is

mediated by thrombopoietin that is mainly produced in the liver. Interestingly, thrombopoietin production and platelet haemostasis is rarely influenced by extrahepatic signals [33].

Reflecting the results of the present study, a therapeutic approach to improve the postoperative outcome by supporting liver regeneration might be the prophylactic application of thrombocytes or thrombocyte-stimulating agents such as thrombopoietin or thrombopoietin-analoga. The application of thrombopoietin has already been tested effectively in thrombocytopenic patients [34-36]. This could be a promising therapeutic option to avoid severe postoperative liver failure by accelerating liver regeneration. Noteworthy, the risk of thrombotic side effects should not be underestimated in patients suffering from malignant disease.

In conclusion, platelets influence the postoperative outcome after liver surgery for liver metastases of colorectal carcinoma. It is suggestive that platelets promote liver regeneration. This might be an interesting therapeutic approach to improve postoperative outcome and avoid liver failure after liver surgery. Clinical trials are needed to test the efficacy of administration of platelets or platelet stimulating factors as thrombopoietin on liver regeneration.

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