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ORIGINAL ARTICLE

# Co-existing liver disease increases the risk of postoperative thrombocytopenia in patients undergoing hepatic resection: implications for the risk of epidural hematoma associated with the removal of an epidural catheter

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**Abstract**
*Purpose* A common surgical diagnosis for hepatic resection in Japan is hepatocellular carcinoma secondary to chronic viral hepatitis. It is known that chronic liver disease causes a decrease in blood platelet count. We retrospectively reviewed the perioperative changes in blood platelet count associated with hepatic resection at a Japanese institution and evaluated the incidence and risk factors for postoperative thrombocytopenia, which may increase the potential risk of epidural hematoma.
*Methods* We analyzed the data of 165 patients who underwent hepatic resection between 1 March 2010 and 30 June 2012 at Hokkaido University Hospital. The criterion of the platelet count for the unsafe removal of epidural catheter was <100,000/μL. Logistic regression was used to model the association between postoperative thrombocytopenia and co-existing liver disease, estimated blood loss and type of hepatic resection.
*Results* After hepatic resection, 42.4 % of patients without preoperative thrombocytopenia experienced thrombocytopenia. The presence of co-existing liver disease was identified as a risk factor for postoperative thrombocytopenia [odds ratio 3.17 (95 % confidence interval 1.63–6.18)]. There was no epidural hematoma in the 149 patients who had epidural anesthesia.
*Conclusion* Hepatic resection can cause postoperative thrombocytopenia that may increase the potential risk of epidural hematoma associated with catheter removal, and the presence of co-existing liver disease heightens concerns for postoperative crucial thrombocytopenia.

**Keywords** Hepatic resection · Co-existing liver disease · Thrombocytopenia · Epidural hematoma

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## Introduction

Continuous epidural anesthesia and analgesia are widely used for postoperative pain relief after hepatic resection in Japan, but several authors have claimed that hepatic resection causes postoperative coagulation abnormality, which may increase the potential risk of epidural hematoma associated with catheter removal [1–5]. In most previous studies assessing the postoperative changes in hemostatic profile after hepatic resection and the risk of epidural hematoma, the surgical diagnoses were metastatic tumors and partial donor hepatectomy [2–4, 6, 7]. However, the disease for which hepatic resection is most commonly performed in Japan is hepatocellular carcinoma [8]. It is well known that hepatocellular carcinoma is secondary to liver diseases including chronic viral hepatitis B and C [9]. Chronic hepatitis and cirrhosis can each cause a decrease in the blood platelet count, even if there is no coagulopathy [10, 11]. Most anesthesiologists believe that epidural anesthesia is unsafe for patients with platelet counts below 80,000–100,000/μL [12–14], although a specific platelet count predictive of neuraxial anesthetic complications has not been determined. Accordingly, it is possible that in patients with chronic liver disease, the incidence of crucial thrombocytopenia after hepatic

resection, which may increase the risk of epidural hematoma associated with catheter removal, may be greater than that in patients without co-existing liver disease. Yuan et al. [5] have reported that in hepatic resection patients, pre-existing liver cirrhosis is a risk factor for abnormalities on postoperative hemostatic tests including prothrombin time, activated partial thromboplastin time, or platelet count values. However, there have been few investigations to assess whether the presence of co-existing liver disease is a risk factor for postoperative thrombocytopenia apart from the risks associated with abnormal coagulation tests.

We retrospectively reviewed the perioperative changes in blood platelet count associated with hepatic resection at a single Japanese institution and evaluated the incidence of postoperative thrombocytopenia that may increase the potential risk of epidural hematoma associated with catheter removal in a surgical population with a high prevalence of liver disease. We also examined whether the presence of co-existing liver diseases is related to crucial thrombocytopenia after hepatic resection.

## Materials and methods

After institutional review board approval, the data of patients who had hepatic resection between 1 March 2010 and 30 June 2012 at the Department of Gastroenterological Surgery I at Hokkaido University Hospital were retrieved from the hospital's computerized clinical information system. Data from donors who had partial hepatic resection were excluded from the present analysis. Information regarding the patients' gender, age, medical history including co-existing liver diseases, Child-Pugh class, perioperative medication, surgical diagnosis, types of hepatic resection, anesthesia procedure, estimated intraoperative blood loss, and perioperative blood product administration were recorded. We collected and analyzed the patients' data regarding blood platelet counts and the prothrombin time international normalized ratio (PT/INR), which were obtained during the preoperative period, immediately after surgery, and over the seven days following surgery. The thrombocytopenia criterion for unsafe removal of the epidural catheter was a platelet count <100,000/μL [12].

Data are expressed as means ± standard deviations (SDs). The unpaired *t* test and Chi square test were used to test the differences in continuous variables and categorical variables between two groups, respectively. Comparisons between the preoperative blood platelet count results and those obtained after hepatic resection were performed by one-way analysis of variance for repeated measures with Dunnett's test. *P* values <0.05 were considered significant. The 95 % confidence interval (CI) for the incidence of epidural hematoma was calculated using the exact Clopper–Pearson method. To determine whether the presence of co-existing liver disease, as well as the amount of intraoperative blood loss and the type (major or minor) of hepatic resection (which have both been suggested to affect the postoperative coagulation profile [2, 4]), are risk factors for crucial thrombocytopenia after hepatic resection, we calculated the univariate odds ratios with corresponding 95 % CIs. We also calculated the adjusted odds ratios for the factors using multivariate logistic regression models. In this study, we defined major hepatic resection as the resection of four or more liver segments [15]. The analyses were performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

## Results

During the study period, a total of 203 patients underwent hepatic resection at the Department of Gastroenterological Surgery I at Hokkaido University Hospital. We excluded 22 patients who had risks of hemostatic disorders not related to liver disease, two patients who had surgical hemostasis for postoperative bleeding, one patient in whom the tumor embolus in the right atrium was removed under cardiopulmonary bypass, and 13 who had preoperative platelet counts <100,000/μL. The most common surgical diagnosis was hepatocellular carcinoma ($n = 93$), followed by metastatic cancer ($n = 21$), echinococossis ($n = 20$), cholangiocellular carcinoma ($n = 13$), biliary and gallbladder malignancy ($n = 13$), and others ($n = 5$). Eighty-two patients had co-existing liver diseases. Sixty-eight patients were chronically infected with hepatitis viruses (hepatitis B $n = 50$, hepatitis C $n = 16$, hepatitis B and C $n = 2$), 11 had alcoholic liver disease, two had non-alcoholic steatohepatitis, and one had liver cirrhosis of unknown etiology. Three patients who had co-existing liver diseases were classified as Child-Pugh class B, and the remaining 79 patients were classified as Child-Pugh class A. Eighty-nine patients had major liver resections, and 76 patients had minor resections.

Changes in the perioperative blood platelet count and the number of patients with postoperative thrombocytopenia are shown in Fig. 1. Seventy patients (42.4 %) had postoperative thrombocytopenia of less than 100,000/μL. Forty-one patients (24.8 %) had severe thrombocytopenia of <80,000/μL and four patients had minimum values of <50,000/μL. The peak number of patients with thrombocytopenia was on postoperative days (PODs) 2 and 3. The data for the patients with normal platelet counts and thrombocytopenia after hepatic resection are summarized in Table 1. The presence of co-existing liver disease was found to be an independent risk factor for

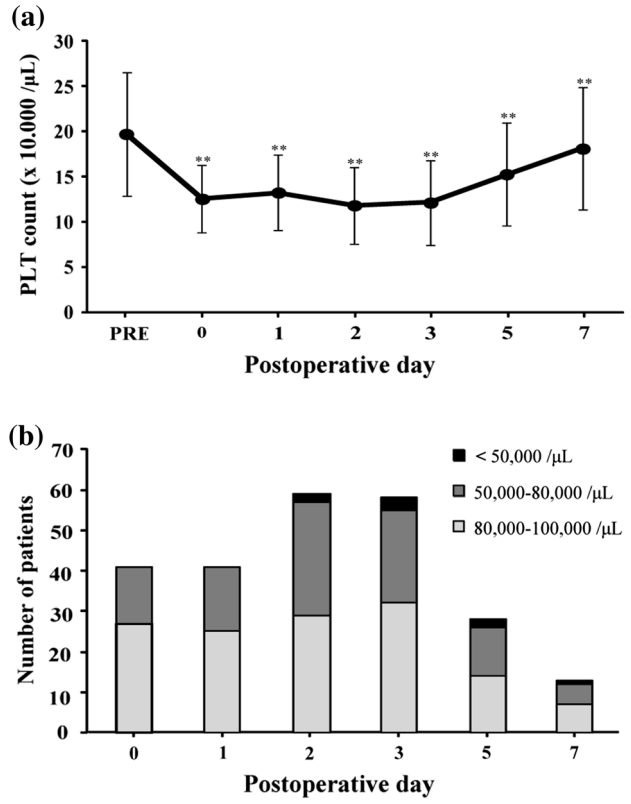


**Fig. 1** **a** Perioperative changes in the blood platelet (PLT) count and **b** the number of patients with thrombocytopenia on postoperative days (PODs). In 13 patients in whom the hemostatic tests were not taken on POD 5 and 7, the data taken on POD 4 and 6 were used as data of POD 5 and 7, respectively. ** $P < 0.01$ vs. preoperative value, *PRE* preoperative

**Table 1** Data for patients with postoperative minimum PLT count ≥100,000 and <100,000/μL

| | Postoperative minimum PLT count | | *P* value |
|---|---|---|---|
| | ≥100,000/μL | <100,000/μL | |
| *N* | 95 | 70 | |
| Age (years) | 62.0 ± 12.4 | 65.4 ± 10.2 | 0.07 |
| Gender (*N*: M/F) | 66/29 | 63/7 | <0.01 |
| Operating time (min) | 332 ± 116 | 360 ± 119 | 0.12 |
| Anesthesia time (min) | 465 ± 135 | 478 ± 125 | 0.52 |
| Estimated intraoperative blood loss (mL) | 585 ± 778 (median 370) | 617 ± 661 (median 425) | 0.78 |
| Number of patients who had PLT transfusion during intra- or postoperative periods | 0 | 4 | 0.02 |
| Number of patients who had FFP transfusion during intra- or postoperative periods | 26 | 34 | 0.05 |
| Preoperative PT/INR | 1.01 ± 0.01 | 1.04 ± 0.01 | 0.04 |
| Postoperative maximum PT/INR | 1.33 ± 0.19 | 1.39 ± 0.24 | 0.08 |
| Number of patients with postoperative maximum PT/INR >1.5 | 17 | 18 | 0.32 |
| Preoperative PLT count (×10,000/μL) | 22.6 ± 6.3 | 15.5 ± 5.2 | <0.01 |
| Postoperative minimum PLT count (×10,000/μL) | 13.6 ± 3.0 | 7.6 ± 1.5 | <0.01 |
| % change[a] | −37.6 ± 12.7 | −48.6 ± 12.7 | <0.01 |

*PLT* platelet, *FFP* fresh frozen plasma, *PT/INR* prothrombin time international normalized ratio

[a] % change = (postoperative minimum PLT count − preoperative PLT count) × 100/preoperative PLT count

thrombocytopenia after hepatic resection (Table 2). In 82 patients with co-existing liver disease, the preoperative platelet counts were significantly lower than those of the patients without liver disease (17.5 ± 6.7 vs. 21.7 ± 6.3/μL, $P < 0.01$) while the % change in the platelet count after surgery in patients with co-existing liver disease was similar to that in the patients without liver disease (−40.8 ± 13.8 vs. −43.7 ± 13.6 %, N.S.).

One hundred forty-nine patients had epidural anesthesia. Epidural catheters were removed on POD 3.8 ± 0.8. There was no epidural hematoma case during the study period (95 % CI of the incidence of epidural hematoma: 0.00–2.44 %).

## Discussion

We found that in our hepatic resection population with the common surgical diagnosis of hepatocellular carcinoma, hepatic resection caused thrombocytopenia at a level at which the removal of the epidural catheter is not considered safe in 42.4 % of the patients with preoperative platelet counts >100,000/μL. We also found that the presence of co-existing liver disease is a risk factor for postoperative crucial thrombocytopenia after hepatic resection.

Although the actual incidence of symptomatic epidural hematoma is unknown, the incidence was estimated on the basis of previous reports as being <1 in 150,000 patients receiving epidural anesthesia [16]. In the present study, there was no symptomatic epidural hematoma case among 149 patients who had epidural anesthesia. However, in light of the small sample size, the current result does not necessarily imply that patients undergoing hepatic resection do not have an increased risk of neuraxial hematoma.

Some studies have evaluated blood platelet count after hepatic resection in terms of the potential risk of epidural hematoma [2–7]. Shontz et al. [4] and Matot et al. [2] reported that the incidence of thrombocytopenia of <100,000/μL after hepatic resection was 18 and 5 %, respectively. Choi et al. [6] reported that five of 360 living liver donors had a platelet count <80,000/μL.

**Table 2** Multivariable logistic regression analysis of factors that are related to thrombocytopenia after hepatic resection

| Variable | Postoperative minimum value of PLT count (/μL) | | Odds ratio (OR) | | | |
|---|---|---|---|---|---|---|
| | ≥100,000 | <100,000 | Univariate OR | *P* value | Adjusted OR | *P* value |
| Liver disease (*N*: +/−) | 35/60 | 47/23 | 3.50 (95 % CI 1.83–6.71) | 0.002 | 3.17 (95 % CI 1.63–6.18) | 0.001 |
| Resection type (*N*: major/minor) | 58/37 | 31/39 | 0.51 (95 % CI 0.27–0.95) | 0.036 | 0.63 (95 % CI 0.32–1.26) | 0.191 |
| Estimated blood loss (*N*: <500 mL/ 500–1,000 mL/more than 1,000 mL) | 56/24/15 | 42/18/10 | 0.99 (per 500 mL) (95 % CI 0.80–1.22) | 0.900 | 1.04 (per 500 mL) (95 % CI 0.82–1.31) | 0.750 |

*PLT* platelet, *95 % CI* 95 % confidence interval

The incidence of thrombocytopenia after hepatic resection in our institution is higher than the incidence in these reports. Most of our patients underwent hepatic resection for hepatocellular carcinoma, which is usually associated with viral hepatitis [9], and half of our patients had chronic liver disease including chronic infection with hepatitis B or C virus. In contrast, in most of the previous studies, hepatocellular carcinoma was not a common surgical diagnosis for hepatic resection, although information about co-existing liver disease was not given [2–4, 6, 7]. Patients with chronic liver disease (chronic viral hepatitis and cirrhosis) present low blood platelet counts which may result from bone marrow suppression, a decrease of liver thrombopoietin production, an autoimmune mechanism, or platelet sequestration within the spleen [10, 11]. The present results revealed the presence of co-existing liver disease as an independent risk factor for thrombocytopenia after hepatic resection, and showed that the higher incidence of postoperative crucial thrombocytopenia in patients with chronic liver diseases is due to the lower preoperative platelet count. Therefore, it is possible that the difference in the incidence of postoperative thrombocytopenia between most previous studies and ours is due to differences in surgical populations. However, Yuan et al. [5] reported that the peak incidence of thrombocytopenia of <100,000/μL after hepatic resection was approximately 10 % on POD 2 in a population in which 44.4 % of the patients had chronic liver disease, although information about preoperative platelet count and the total number of patients with postoperative thrombocytopenia were not given. It is not yet clear why our present result differs from theirs.

In the present study, the incidence of patients who had a thrombocytopenia <100,000/μL reached a peak of 35 % on PODs 2 and 3. This finding is in accord with the previous reports showing that the platelet count after hepatic resection reaches a nadir on POD 2–3 [2, 3, 6, 7]. It must be noted that on POD 7, about 8 % of our patients still had thrombocytopenia to an extent that epidural catheter removal was not considered safe. These findings suggest that there is an increased risk of epidural hematoma associated with catheter removal for 1 week after hepatic resection.

Our study has limitations associated with its retrospective and observational design. The major issue for this study assessing hemostatic profiles is the lack of defined criteria for perioperative transfusions of fresh frozen plasma (FFP) and platelets. In this patient population, FFP and platelets were transfused during intra- and postoperative periods at the discretion of the anesthesiologists and surgeons in charge; 36 % of our patients had FFP transfusion. Accordingly, the postoperative coagulation data such as the PT/INR are difficult to interpret in this study. However, the patients who received platelet transfusion were few (only four of 165). We therefore think that this issue does not complicate the interpretation of the present results regarding the perioperative platelet count.

In summary, hepatic resection can cause postoperative thrombocytopenia that may increase the potential risk of epidural hematoma associated with catheter removal. In particular, it should be noted that the presence of co-existing liver disease along with a lower preoperative platelet count may heighten concerns regarding postoperative crucial thrombocytopenia.

## References

1. Fazakas J, Tóth SZ, Füle B, Smudla A, Mándli T, Radnai M, Doros A, Nemes B, Kóbori L. Epidural anesthesia? No of course. Transplant Proc. 2008;40:1216–7.
2. Matot I, Scheinin O, Eid A, Jurim O. Epidural anesthesia and analgesia in liver resection. Anesth Analg. 2002;95:1179–81.
3. Siniscalchi A, Begliomini B, De Pietri L, Braglia V, Gazzi M, Masetti M, Di Benedetto F, Pinna AD, Miller CM, Pasetto A. Increased prothrombin time and platelet counts in living donor right hepatectomy: implications for epidural anesthesia. Liver Transpl. 2004;10:1144–9.
4. Shontz R, Karuparthy V, Temple R, Brennan TJ. Prevalence and risk factors predisposing to coagulopathy in patients receiving epidural analgesia for hepatic surgery. Reg Anesth Pain Med. 2009;34:308–11.

5. Yuan FS, Ng SY, Ho KY, Lee SY, Chung AY, Poopalalingam R. Abnormal coagulation profile after hepatic resection: the effect of chronic hepatic disease and implications for epidural analgesia. J Clin Anesth. 2012;24:398–403.
6. Choi SJ, Gwak MS, Ko JS, Kim GS, Ahn HJ, Yang M, Hahm TS, Lee SM, Kim MH, Joh JW. The changes in coagulation profile and epidural catheter safety for living liver donors: a report on 6 years of our experience. Liver Transpl. 2007;13:62–70.
7. Stamenkovic DM, Jankovic ZB, Toogood GJ, Lodge JPA, Bellamy MC. Epidural analgesia and liver resection: postoperative coagulation disorders and epidural catheter removal. Minereva Anestesiol. 2011;77:671–9.
8. Easton A. Liver cancer toll high in Japan. BMJ. 1999;318:1510.
9. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245–55.
10. Pluta A, Gutkowski K, Hartleb M. Coagulopathy in liver diseases. Adv Med Sci. 2010;55:16–21.
11. Olariu M, Olariu C, Olteanu D. Thrombocytopenia in chronic hepatitis C. J Gastrointestin Liver Dis. 2010;19:381–5.
12. Fischer SP, Bader AM, Sweitzer B. Preoperative evaluation. In: Miller RD, editor. Miller's anesthesia, vol 1. 7th ed. Philadelphia: Churchill Livingstone; 2010. p. 1001–66.
13. Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anesth Analg. 1994;79:1165–77.
14. van Veen JJ, Nokes TJ, Makris M. The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopenic individuals. Br J Haematol. 2010;148:15–20.
15. Reddy SK, Barbas AS, Turley RS, Steel JL, Tsung A, Marsh JW, Geller DA, Clary BM. A standard definition of major hepatectomy: resection of four or more liver segments. HPB. 2011;13:494–502.
16. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan C-S. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy; American society of regional anesthesia and pain medicine evidence-based guidelines (third edition). Reg Anesth Pain Med. 2010;35:64–101.