

# Predictive Ability of Preoperative PT-INR and Postoperative MCP1 for Post-hepatectomy Liver Failure

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**Abstract.** *Background:* We sought a diagnostic tool using perioperative variables that might predict post-hepatectomy liver failure (PHLF). *Patients and Methods:* In 68 patients undergoing major hepatectomy, data on inflammatory markers and coagulation factors were prospectively collected and were compared between patients with International Study Group of Liver Surgery definition grade B/C PHLF (LF group) and those without LF (non-LF group). *Results:* Preoperatively, the LF group (n=9; 13.2%) had a lower platelet count and a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity and a higher prothrombin time-International Normalized Ratio (PT-INR) than the non-LF group. On postoperative day 1, the LF group had significantly higher serum interleukin 6 (IL6), C-C motif chemokine ligand 2 (CCL2), and IL10 levels than the non-LF group. The logistic regression model that included preoperative PT-INR and CCL2 on postoperative day 1 predicted grade B/C PHLF with 100% sensitivity and 89.8% specificity. *Conclusion:* Our findings suggest that the combination of preoperative PT-INR and CCL2 on postoperative day 1 can predict PHLF earlier and precisely after major hepatectomy.

Although hepatectomy can currently be performed quite safely due to remarkable refinements in surgical techniques, perioperative management, and surgeon experience, the morbidity and mortality rates after major hepatectomy remain 30-45% and 3-5%, respectively (1-5). Post-hepatectomy liver failure (PHLF) particularly easily leads to mortality. Therefore, various models using preoperative

variables have been devised to predict PHLF (6-9). However, PHLF cannot be completely prevented using these existing models.

The International Study Group of Liver Surgery (ISGLS) proposed a definition of PHLF in 2011 (10) that had reliable prognostic value, as ISGLS grade B/C PHLF often led to severe morbidity or mortality (11). However, the diagnosis of PHLF based on the ISGLS definition as well as other established criteria, such as the 50-50 criteria (12) or  $\text{Peak Bili} > 7$  criteria (13), requires about 5 days to have elapsed after hepatectomy, by which point it may be too late to intervene (10-13). Even though treatments of PHLF itself have not been established, the outcomes of hepatectomy might be improved by prevention or earlier intervention if a diagnostic tool for predicting PHLF much earlier than postoperative day (POD) 5 can be constructed.

LF is considered multifactorial and often associated with sepsis (14-16). Immediate responses of various inflammatory and coagulation markers, such as interleukin-6 (IL6) or plasminogen activator inhibitor-1 (PAI1), have been reportedly involved in the development of severe sepsis and significantly correlated with the treatment outcomes (17-21). Furthermore, such immediate responses have been observed in the early phase after hepatectomy and are significantly associated with the development of PHLF (22-24).

We considered that such immediate responses after hepatectomy have a significant role in developing PHLF, as well as predictive value for PHLF, especially in combination with preoperative variables. In the present study, we investigated the chronological changes in perioperative variables, including inflammatory cytokines, coagulation, and fibrinolytic factors, in order to construct a diagnostic model for predicting PHLF precisely and much earlier than POD5.

## Patients and Methods

The perioperative variables of 68 patients undergoing major hepatectomy, including right or left hemi-hepatectomy and right or left trisectionectomy, between October 2013 and October 2015 at the Yokohama City University Hospital were investigated. The

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**Key Words:** Major hepatectomy, post-hepatectomy liver failure, predictive model, inflammatory marker, coagulation factor.

Table I. Clinical characteristics of patients in the groups with post-hepatectomy liver failure (LF) and without (non-LF).

Variable		Total n=68	LF group n=9	Non-LF group n=59	p-Value
Age, years	Mean±SD	62±16	66±10	61±16	0.751
Gender, n (%)	Male	43 (63%)	6 (67%)	37 (63%)	0.819
Disease, n (%)	Cholangiocarcinoma	32 (47%)	5 (56%)	27 (46%)	
	Hepatocellular carcinoma	11 (16%)	1 (11%)	10 (17%)	
	Liver metastasis	13 (19%)	2 (22%)	11 (19%)	0.801
	LDLT donor	5 (7%)	1 (11%)	4 (7%)	
	Other	7 (10%)	0	7 (12%)	
Liver function	ICG-R15, %	12.9±5.9	16.5±7.5	12.3±5.5	0.128
	Serum total bilirubin, mg/dl	0.6±0.3	0.9±0.67	0.61±0.21	0.151
	Serum albumin, g/dl	3.3±0.5	3.0±0.5	3.4±0.4	<b>0.030</b>
	PT-INR	1.1±0.1	1.21±0.15	1.08±0.08	<b>0.009</b>
Preoperative cholangitis, n (%)	Yes	18 (26%)	3 (33%)	15 (25%)	0.616
Preoperative treatment, n (%)	Chemotherapy	25 (37%)	5 (56%)	20 (24%)	0.209
	Portal vein embolization	33 (49%)	5 (56%)	28 (48%)	0.651
	Preoperative biliary drainage	23 (34%)	4 (44%)	19 (32%)	0.470
	Anticoagulant therapy	9 (13%)	1 (11%)	8 (14%)	0.840
Preoperative planning, mean±SD	Resection volume, ml	510±239	615±289	494±229	0.222
	Resection rate, %	44±15	53±13	42±15	0.054
	Remnant liver volume, ml	634±238	502±106	654±247	0.054
	Predictive score	32±22	49±13	30±22	<b>0.012</b>
	rICGK	0.08±0.03	0.06±0.01	0.08±0.03	<b>&lt;0.001</b>
Procedure, n (%)	Right hemi-hepatectomy	31 (46%)	4 (44%)	27 (46%)	0.941
	Left hemi-hepatectomy	27 (40%)	2 (22%)	25 (42%)	0.250
	Right trisectionectomies	4 (6%)	1 (11%)	3 (5%)	0.474
	Left trisectionectomies	6 (9%)	2 (22%)	4 (7%)	0.128
Additional procedure, n (%)	Pancreatico-duodenectomy	5 (7%)	0	5 (9%)	0.364
	Biliary tract reconstruction	27 (40%)	5 (56%)	22 (37%)	0.297
	Blood vessel reconstruction	24 (35%)	6 (67%)	18 (31%)	<b>0.034</b>
Intraoperative factors	Operative time, min	656±230	859±362	625±188	0.078
	Bleeding, ml	1407±1020	3321±3404	1115±702	0.189
	RCC transfusion, ml	329±748	1307±1615	180±340	<b>&lt;0.001</b>
Morbidity, n (%)	Total	19 (28%)	5 (56%)	14 (24%)	<b>0.047</b>
	Infection	11 (16%)	3 (33%)	8 (14%)	0.310
	Bleeding	6 (9%)	2 (22%)	4 (7%)	0.128
	Thrombosis	0	0	0	0.694
	Other	4 (6%)	0	4 (7%)	0.421
Length of hospital stay, days	Mean±SD	21±20	47±43	17±3	<b>0.025</b>
In-hospital mortality	Frequency, %	3 (4%)	3 (33%)	0	<b>&lt;0.001</b>

LDLT: Living donor liver transplantation; ICG-R15; ICG retention rate at 15 minutes; PT-INR: prothrombin time-International Normalized Ratio; rICGK: Indocyanine green kinetics value for the liver remnant [=ICG K (ICG plasma disappearance rate)×remnant liver rate]; RCC: red-blood cell concentrate. Bold values show significance.

patient characteristics are summarized in Table I. Twenty-five patients (37%) underwent pre-hepatectomy chemotherapy. Twenty-seven patients (40%) had biliary reconstruction. Twenty-four patients (35%) had concomitant vascular resection and reconstruction. Five patients (7%) underwent concomitant pancreaticoduodenectomy. Written-informed consent, as approved by the Human Research Review Committee of Yokohama City University Hospital (no. 131107018), was obtained from all patients prior to their enrollment in our study.

**Preoperative management.** We judged hepatectomy to have been performed with acceptable safety when the following criteria were fulfilled: Indocyanine green kinetics value for the liver remnant (rICGK) (9) of more than 0.05 and more than 300 ml of functional

liver remnant. The liver and tumor volume were measured by computed tomographic volumetry (25). Portal vein embolization (PVE) was performed before right hepatectomy and before right or left trisectionectomy.

**Blood sampling and measurement of pro-/anti-inflammatory markers and coagulation/fibrinolysis factors.** Peripheral blood samples were obtained before the operation and on POD1, 3, and 5. In addition to usual laboratory tests in daily clinical practice, the following pro- and anti-inflammatory cytokines, coagulation, and fibrinolytic factors were measured at each time point: IL1β, C-C motif chemokine ligand 2 (CCL2), IL6, activities of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13), and von Willebrand factor (vWF).

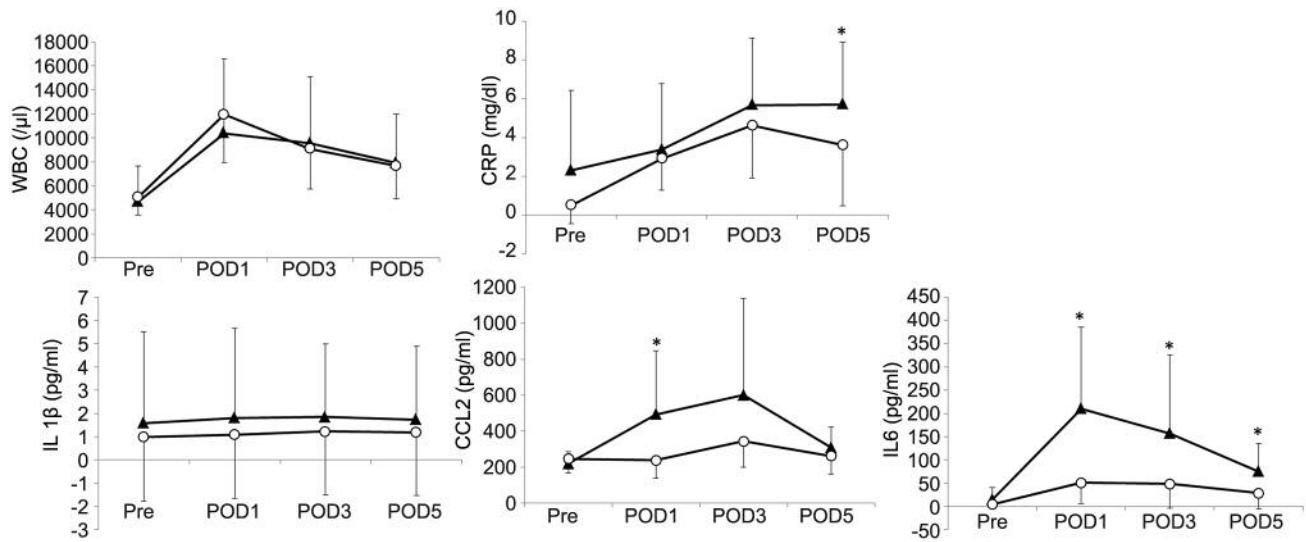


Figure 1. Changes in the inflammatory markers in the groups with (triangles) and without (circles) post-hepatectomy liver failure. The values are expressed as the mean  $\pm$  standard deviation. WBC: White blood cell count; CRP: C-reactive protein; IL1 $\beta$ : interleukin 1 $\beta$ ; CCL2: C-C motif chemokine ligand 2; IL6: interleukin 6; POD: postoperative day; Pre: pre-operative. \*Significantly different at  $p < 0.05$ .

The serum levels of IL6 were quantified using a two-step sandwich chemiluminescence enzyme immunoassay method. The serum levels of IL1 $\beta$  (Quantikine HS human IL-1 $\beta$  Immunoassay; R&D Systems, Minneapolis, MN, USA) and CCL2 (Quantikine Human MCP-1 Immunoassay; R&D Systems) were quantified using enzyme-linked immunosorbent assays. ADAMTS13 activity was measured using a chromogenic substrate (26). The level of vWF activity was measured using the fixed-platelet aggregation method. The prothrombin time international normalized ratio (PT-INR) was measured using a method designed by Quick (HemosIL RecombiPlasTin; Japan, Tokyo, Japan). Plasma fibrinogen levels were measured using the Clauss method (HemosIL Fib, Japan). Plasma fibrin and fibrinogen degradation products-E (FDP-E) levels were measured using a latex photometric immunoassay (LPFA FDP-E; LSI Medience, Tokyo, Japan). These assays were conducted in accordance with the manufacturer's instructions.

PHLF was diagnosed according to the ISGLS definition (10). The above-stated perioperative variables were compared between patients with ISGLS grade B/C PHLF (LF group) and those without LF.

**Statistical analyses.** Statistical analyses were performed using the SPSS statistical software version 22.0.0 (IBM, Armonk, NY, USA). Categorical variables were compared using the chi-squared test. Continuous variables are expressed as the mean  $\pm$  standard deviation, and differences were assessed by the Mann-Whitney *U*-test. Correlation coefficients were calculated with Spearman's rank correlation test when necessary. To determine the influence of different variables on the outcome, a logistic regression analysis was performed. *p*-Values of less than 0.05 were considered statistically significant. To identify the most predictive combination among promising preoperative and POD1 markers, a receiver operating characteristic (ROC) analysis was performed using bivariate logistic regression.

## Results

**Incidence of PHLF.** PHLF was diagnosed in 10 (14.7%) patients (Table I): Grade A in one (1.5%); grade B in five (7.4%); and grade C in four (5.9%). Thus, the 68 patients were divided into clinically relevant LF ( $n=9$ ) and non-LF ( $n=59$ ) groups.

**Clinical characteristics.** The results of a comparison between the LF and non-LF groups are shown in Table I. Preoperatively, the LF group had poor nutritional status, as indicated by low serum albumin, and prolonged coagulation, as indicated by high PT-INR. The application of preoperative interventions, such as chemotherapy, PVE, or biliary drainage, did not differ markedly between the groups. The resection rate was higher ( $p=0.054$ ), and functional liver remnant based on the computed tomographic volumetry was marginally lower ( $p=0.054$ ) in the LF group. In the LF group, the Hyogo University predictive score (8) was higher and the rICGK (9) was significantly lower than in the non-LF group. Concomitant vascular resection and reconstruction was significantly more common in the LF group than in the non-LF group. The operative time and amount of bleeding did not differ markedly between the groups. The volume of intraoperative transfusion of red-blood cell concentrate (RCC) was significantly larger in the LF group than in the non-LF group. The LF group showed significantly more frequent morbidity, defined as postoperative complications with a Dindo-Clavien classification of grade 3 or worse (27), and mortality than the non-LF group. Grade B/C PHLF led to mortality in three of nine (33%) patients. One

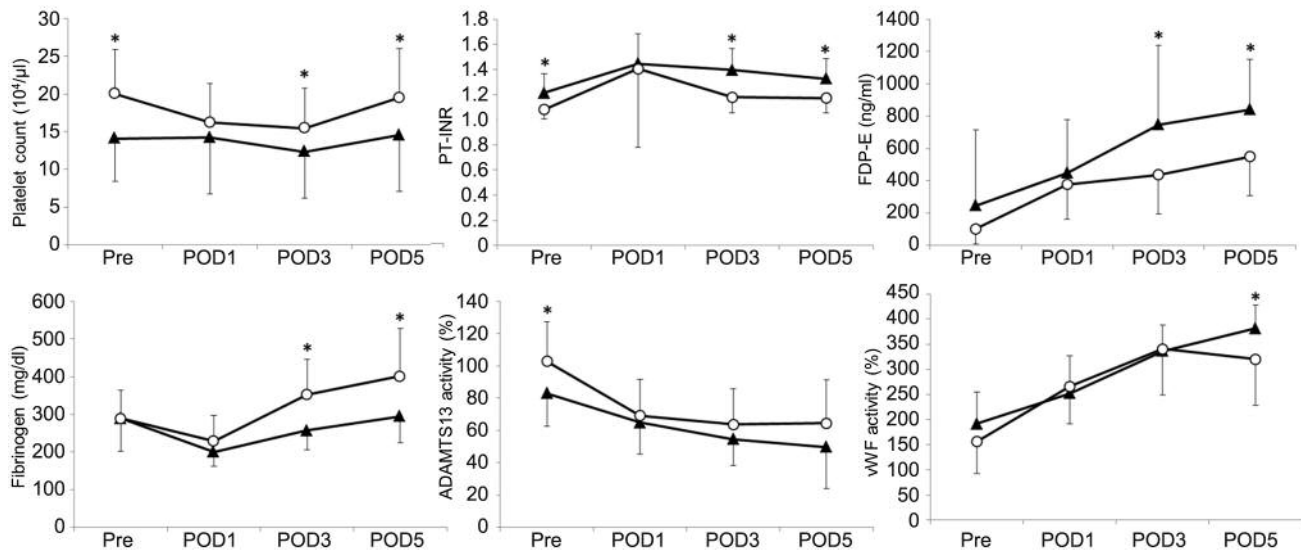


Figure 2. Changes in coagulation and fibrinolytic factors in the groups with (triangles) and without (circles) post-hepatectomy liver failure. The values are expressed as the mean ± standard deviation. PT-INR: Prothrombin time-international normalized ratio; FDP-E: fibrin and fibrinogen degradation products-E; ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; vWF: von Willebrand factor; Pre: pre-operative; POD: postoperative day. \*Significantly different at  $p < 0.05$ .

patient with grade C PHLF died of severe infection following PHLF. One patient with grade B PHLF died of sepsis due to liver abscess. Another patient with grade B PHLF died of massive intraperitoneal bleeding.

**Inflammatory markers.** The preoperative inflammatory markers were quantitatively similar for the two groups (Figure 1). However, the levels of CCL2, IL6, and IL10 on POD1 were significantly higher in the LF group than in the non-LF group. In the LF group, the IL6 and IL10 levels peaked at POD1, and the CCL2 level peaked at POD3. No marked difference in the level of these markers was observed on POD5, except for IL6, which was still significantly higher at POD5 in the LF group than in the non-LF group. The white blood cell count and IL1 $\beta$  level did not differ markedly between the groups at any time points.

**Coagulation and fibrinolytic factors.** The preoperative platelet count and ADAMTS13 activity were significantly lower and the PT-INR significantly higher in the LF group than in the non-LF group (Figure 2). Although no differences were observed at POD1, the differences reached significance again on POD3 and thereafter. Furthermore, the FDP-E on POD3 and 5 and vWF activity on POD5 were higher in the LF group than in the non-LF group, although these factors did not differ significantly between the groups until POD1.

**Construction of predictive models.** ROC analyses were performed for variables that showed significant differences

between the two groups in order to determine the cut-off value for discriminating between the groups (Table II). The following variables were therefore selected as the strongest indicators of grade B/C PHLF among the pre-, intra-, and immediately postoperative variables: rICGK, volume of RCC during surgery, and total bilirubin (T-Bil) on POD1. The preoperative platelet count and T-Bil on POD1 had high specificity, while the rICGK, RCC volume, CCL2 and T-Bil values on POD1 had the highest sensitivity (88.9%).

To further improve the sensitivity and specificity, combination analyses were performed using bivariate logistic regression, with bivariate combination considered statistically valid based on the sample size and the incidence of PHLF. Combinations correlating significantly with each other were excluded. Combinations that were not independent of each other were also excluded. The Youden index of each combination is shown in Table III. The combination of preoperative PT-INR and CCL2 on POD1 gave the largest Youden index (0.898), indicating that this combination had the strongest ability to predict grade B/C PHLF at POD1.

Figure 3 shows the cut-off value calculated by the Youden index, which is illustrated by the red line. The formula for the cut-off line for predicting grade B/C PHLF was as follows: (Preoperative PT-INR) + (0.00079 × CCL2 on POD1) = 1.37. Nine out of 15 patients (60%) above this line developed PHLF. This predictive model had a sensitivity of 100%, specificity of 90%, positive predictive value of 60%, and negative predictive value of 100%.

Table II. A receiver operating characteristics analysis of the preoperative and postoperative day 1 variables.

Variable		AUC	Cut-off value	95% CI	Sensitivity	Specificity
Preoperative	Predictive score	42.65	0.762	0.617-0.908	77.8%	65.5%
	rICGK	0.06	0.880	0.759-1.000	88.9%	86.4%
	Serum albumin, g/dl	2.85	0.725	0.536-0.914	55.6%	89.8%
	Platelet count, 10 <sup>4</sup> /μl	12.25	0.755	0.576-0.935	55.6%	93.2%
	PT-INR	1.135	0.770	0.555-0.986	77.8%	78.0%
	ADAMTS13 activity, %	94	0.727	0.559-0.895	77.8%	62.7%
Intra-operative POD1	RCC transfusion, ml	140	0.845	0.711-0.997	88.9%	71.2%
	IL6, pg/ml	106.5	0.791	0.562-1.000	77.8%	91.5%
	CCL2, pg/ml	241.5	0.805	0.650-0.960	88.9%	59.3%
	AST, IU/l	438	0.712	0.487-0.937	66.7%	76.3%
	T-Bil, mg/dl	2.95	0.929	0.853-1.000	88.9%	94.9%

AUC: Area under the receiver operating characteristics curve; CI: confidence interval; rICGK: indocyanine green kinetics value for the liver remnant [=ICG K (ICG plasma disappearance rate)×remnant liver rate]; PT-INR: prothrombin time-international normalized ratio; ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; RCC: red-blood cell concentrate; IL6: interleukin 6; CCL2: C-C motif chemokine ligand 2; AST: aspartate aminotransferase; T-bil: total bilirubin. Predictive score [=−84.6+0.933×resection rate+1.11×ICGR15+0.999×age] (8).

Table III. A receiver operating characteristics analysis using a bivariate logistic regression analysis of all combination with preoperative and markers on postoperative day 1 (POD1).

		Preoperative					Intra-operative		POD1		
		rICGK	Alb	Plt	PT-INR	ADAMTS13	RBC	IL6	CCL2	AST	T-Bil
Preoperative	Predictive score	a	b	0.655	0.741	c	0.709	c	0.571	0.475	c
	rICGK		c	0.780	0.71	0.736	0.744	c	0.744	0.71	0.838
	Alb			0.686	c	c	c	c	0.616	0.616	c
	Plt				0.72	0.601	0.71	0.838	0.761	0.635	0.864
	PT-INR					0.744	0.797	b	0.898	0.821	b
	ADAMTS13						0.659	c	0.633	0.505	c
Intraoperative POD1	RCC transfusion							b	a	c	b
	IL6								b	0.744	b
	CCL2									c	0.753
	AST										0.821

rICGK: Indocyanine green kinetics value for the liver remnant [=ICG K (ICG plasma disappearance rate)×remnant liver rate]; Alb: albumin; Plt: platelet count; PT-INR: prothrombin time-international normalized ratio; ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; RCC: red-blood cell concentrate; IL6: interleukin 6; CCL2: C-C motif chemokine ligand 2; AST: aspartate aminotransferase; T-Bil: total bilirubin. Predictive score [=−84.6+0.933×resection rate+1.11×ICGR15+0.999×age] (8); The values represent the Youden index of each combination. <sup>a</sup>Combinations that had strong correlations with each other ( $r>0.8$ ). <sup>b</sup>Combinations that had medium correlations with each other ( $r>0.4$ ). <sup>c</sup>Combinations that were not independent of each other according to a bivariate logistic regression analysis ( $p>0.1$ ).

## Discussion

The present study showed that the incidence of grade B/C PHLF was significantly associated with reduced platelet count and ADAMTS13 activity and increased PT-INR in the preoperative period, and with increased CCL2 and IL6 levels on POD1. These findings corroborated the notion that preoperative increased coagulation and postoperative excessive inflammation were significantly associated with the development of PHLF. Furthermore, the present study demonstrated that the predictive model combining the

preoperative PT-INR value and the CCL2 value at POD1 had the strongest ability to predict PHLF, suggesting that the combination of several markers indicative of the coagulation status and immediate inflammatory response may be useful for predicting PHLF earlier and more precisely than existing models.

In addition to the existing models using preoperative variables alone (6-9), numerous preoperative indicators have been reported as promising for predicting or preventing PHLF (28-32). Furthermore, intraoperative factors, such as the need for blood transfusion during surgery (30), have been reported

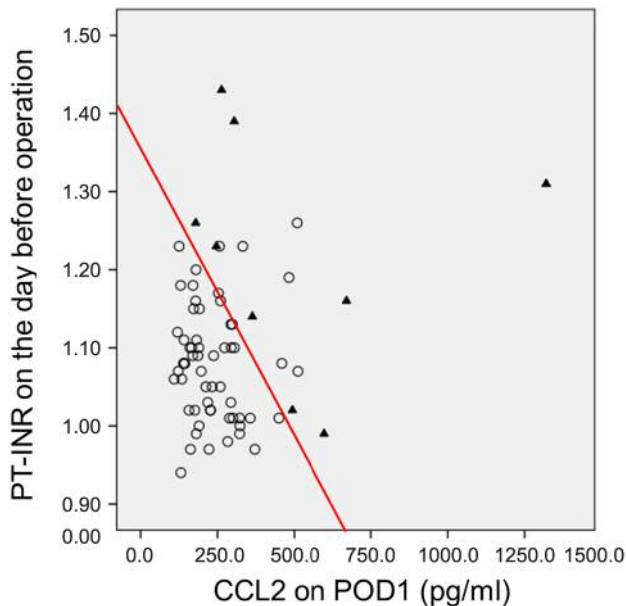


Figure 3. The combination of preoperative prothrombin time/International Normalized Ratio (PT-INR) and C-C motif chemokine ligand 2 (CCL2) on postoperative day 1 in the groups with (triangles) and without (circles) post-hepatectomy liver failure. The straight line represents the formula for predicting grade B/C post-hepatectomy liver failure. Nine out of 15 patients (60%) above this line developed post-hepatectomy liver failure.

to be significantly associated with PHLF. In addition, immediate postoperative factors have been considered to affect the incidence of PHLF significantly (4, 5, 14, 23, 33, 34). Based on these findings, PHLF is considered to be brought about by underlying conditions as well as other factors (*i.e.* pre-, intra-, and immediate postoperative variables).

In brief, the etiology of PHLF is considered multifactorial as well as multiphasic. However, existing models have not included variables at different time phases. We therefore attempted to combine time-phasically different variables to predict PHLF more precisely than the existing models. Although our most promising model, the combination of preoperative PT-INR and CCL2 on POD1, did not include any intraoperative variable, the amount of RCC transfusion during surgery, which was significantly associated with grade B/C PHLF in the present study, was significantly correlated with the CCL2 level on POD1. Thus, the intraoperative events were considered to be reflected in our model. Furthermore, several other combinations, such as the preoperative platelet count and IL6 on POD1, preoperative platelet count and T-bil on POD1, and rICGK and T-bil on POD1, yielded a high Youden index almost equal to that of the most predictive model. These findings support the reasonableness of our idea of combining variables from different time phases.

CCL2 is a chemokine produced by and endothelial cells that promotes the migration of monocytes/macrophages (35). The increased expression of CCL2 was reported to correlate with postoperative complications and organ dysfunction following hepatectomy (36, 37). Furthermore, liver expression of CCL2 was reported to promote fibrosis and to be significantly correlated with either accompanying neutrophil infiltration or disease severity in a model of nonalcoholic steatohepatitis (38-40). In other words, CCL2 strongly affects liver injury and regeneration by its ability to induce the infiltration of neutrophils into the liver parenchyma as well as to promote fibrosis. Thus, controlling the CCL2 expression or excessive accumulation of polymorph nuclear leukocytes in the liver may help resolve PHLF.

Although only bivariate combinations were attempted in the present study due to the sample size and the rate of PHLF occurrence, the present study results suggested the promise of several other markers. ADAMTS13 is a specific cleaving protease for vWF. Reduced activity of ADAMTS13 has been shown in patients with liver schirrous (41) and acute LF (42). In fact, reduced ADAMTS13 activity in the preoperative period was significantly associated with PHLF in the present study. In addition, IL6 is well known to be correlated with liver injury/regeneration after hepatectomy (43). Indeed, an increased serum IL6 level was significantly associated with PHLF in the present study. Therefore, we are currently constructing a prospective database to enable the combination of three or more variables.

Although some substances, such as prostaglandin E<sub>1</sub> (44), have been reported to be effective for treating PHLF, established treatments for PHLF itself have not yet been reported. However, we feel that the earlier identification of PHLF is very important and useful for several reasons. As stated above, the development of PHLF is considered to be multifactorial as well as multiphasic. Thus, earlier intervention based on the risk stratification for PHLF before a definitive diagnosis of PHLF is obtained may help improve the survival outcomes of hepatectomy. Furthermore, the meticulous correction of trivial changes that are usually overlooked in daily practice may be of significant aid in preventing PHLF in high-risk patients. As such, our attempt to diagnose PHLF much earlier than POD5 seems quite useful in terms of the availability of earlier intervention and risk stratification for PHLF.

This study had several limitations. Firstly, the sample size was very small. Furthermore, the present study cohort was heterogenous in terms of the indications for hepatectomy, background liver status, and preoperative treatments, such as biliary drainage, PVE, anticoagulation for thrombotic diseases, and various pre-hepatectomy chemotherapy used. Ideally, the influence of these variables should be assessed individually; however, the small sample size did not allow

for such an investigation. Secondly, the inflammatory markers and coagulation factors were assessed only in serum in the present study. The changes in the expression of these markers in the liver itself should have also been assessed. However, serial liver sample extraction seemed not only impractical but also quite invasive and risky. We therefore abandoned it. Thirdly, it was only possible to examine bivariate combinations in the present study. As stated above, the combination of three or more variables may enable a more accurate prediction than our most promising model.

However, despite these limitations, our predictive model has higher sensitivity and specificity than previous ones, which supports the validity of our idea to construct models using variables in different time phases.

In conclusion, the combination analyses of preoperative coagulation factor and immediate postoperative inflammatory cytokines seems effective for predicting PHLF earlier and more precisely than existing models. We feel that our concept of combining multiphasic variables in order to predict PHLF earlier and more precisely than the existing models is valuable.

## Conflicts of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The Authors declare no conflicts of interest in regard to this study.

## Authors' Contributions

I.E., R.M. and Y.S. designed the study. S.A., Y.S. and K.G. acquired the data. S.A., R.M., R.M., M.T. and I.E. analyzed and interpreted the data. S.A. wrote the draft. D.M. and I.E. revised the article critically.

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