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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

A Novel Clinical Factor, D-Dimer Platelet Multiplication, May Predict Postoperative Recurrence and Prognosis for Patients with Cholangiocarcinoma

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ABSTRACT

Background. Patients with cholangiocarcinoma (CC) have a poor prognosis, and their postoperative survival depends on cancer progression and recurrence. Thus, prognostic markers are needed. The fibrin cleavage product, D-dimer, is associated with malignant progression and recurrence in various cancers, and platelets also are related to tumor progression. This study therefore evaluated a new prognostic factor, D-dimer platelet multiplication (PDM), for predicting prognosis in cases of CC.

Methods. This study retrospectively evaluated 55 cases to determine the correlations of D-dimer, platelet, and PDM levels with patient survival. The cutoff values for D-dimer, platelets, and PDM levels were determined using receiver operating characteristic curve analyses.

Results. The recurrence group exhibited significantly higher D-dimer ($P = 0.00075$) and PDM ($P = 0.0000683$) levels and a trend toward higher platelet levels ($P = 0.117$). The optimal cutoff values were 1.3 μg/mL for D-dimer levels, 245 × 104/μL for platelet levels, and 158.2 × 104 μg/mL × μL for PDM levels. Poor recurrence-free survival was associated with high D-dimer levels ($P = 0.0428$), high platelet levels ($P = 0.0498$), and high PDM levels ($P = 0.00511$). Poor cancer-specific survival was associated with high platelet levels ($P = 0.0156$) and high PDM levels ($P = 0.0156$). In the multivariate analysis, PDM had the greatest correlation with CC prognosis and independently predicted recurrence ($P = 0.00649$).

Conclusion. High D-dimer, platelet, and PDM levels were associated with poor recurrence-free and cancer-specific survivals, with PDM exhibiting the greatest correlation with prognosis. Therefore, PDM may help to predict recurrence and prognosis for patients with CC.

Cholangiocarcinoma (CC) can be categorized as intra- or extrahepatic disease, with the latter category consisting of hilar or bile duct tumors. Unfortunately, CC is associated with a poor prognosis, and its incidence and mortality rates are increasing worldwide.[1] The 5-year survival rates for cholangiocarcinoma are 10 % to 40 %,[2] and surgery is the only effective curative treatment for CC, although postoperative survival is dependent on recurrence.[3,4] Therefore, to improve patients' prognoses, we must understand the mechanism of cancer progression and identify prognostic markers for CC.The fibrin cleavage product, D-dimer, is a clinically important marker used to diagnose pulmonary thromboembolism.[5] Furthermore, recent reports show D-dimer levels to be highly related to various types of human malignancy. Moreover, D-dimer levels are correlated with tumor progression, recurrence, and prognosis in lung cancer,[6,7] prostate cancer,[8] gastric cancer,[9] colorectal cancer.[10,11] Thus, D-dimer levels may be a prognostic marker for CC, although, to the best of our

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knowledge, this relationship has not been evaluated. Several studies also have reported that platelets are associated with cancer progression, recurrence, and prognosis.[12] Therefore, we established a new parameter, D-dimer platelet multiplication (PDM), based on the assumption that multiplying these two factors would provide a better predictive value.Frequently, CC can complicate cholangitis and lead to a poor prognosis. Okuno et al.[13] also have reported that the modified Glasgow Prognostic Score (mGPS), a measure of systemic inflammation, is related to a poor prognosis in hilar CC and reflects cholangitis. Therefore, we evaluated the relationships between D-dimer levels, platelet counts, and inflammation markers as predictive biomarkers in cases of primary CC. Furthermore, we evaluated the associations of D-dimer, platelet, and PDM levels with clinicopathologic factors, inflammatory factors, and patient survival in cases of CC. We also investigated CD42b expression in CC specimens as a marker of local platelet activation at the tumor because CD42b is a glycoprotein marker of platelet activation.

MATERIALS AND METHODS

Patients and Specimens

We retrospectively evaluated consecutive patients with intra- or extrahepatic CC who underwent curative resection in our department during 2005–2015 (Supplementary Table 1). These cases included 34 patients with extrahepatic CC, 11 patients with hilar CC, and 10 patients with intrahepatic CC. The patients ranged in age from 36 to 84 years.

All data (e.g., D-dimer levels and platelet counts) were collected within 1 month before surgery. The surgical techniques were pancreaticoduodenectomy (31 cases), hepatectomy (22 cases), and hepatopancreatoduodenectomy (2 cases). Tumor staging was performed based on the seventh edition of the Union for International Cancer Control tumor-node-metastasis (TMN) criteria. All the patients provided written informed consent for treatment and analyses, and the study's design was approved by our Clinical Ethics Committee (http://ciru.dept.showa.gunma-u.ac.jp/guidance/storage-sample/list.html).

Immunohistochemical Staining

We cut 4-μm sections from paraffin blocks of the CC specimens and mounted the sections of silane-coated glass slides. The slides were subsequently deparaffinized and soaked for 30 min at room temperature in 0.3 % H_2O_2/methanol to block endogenous peroxidases. The sections then were heated in boiled water and Immunosaver (Nishin EM, Tokyo, Japan) at 98 °C for 45 min. Nonspecific binding sites were blocked by incubating the specimens for 30 min with serum-free Protein Block (DAKO, Carpinteria, USA). A rabbit polyclonal anti-CD42b antibody (Abcam, Cambridge, UK) was applied at a 1:100 dilution for 24 h at 4 °C and then visualized using the Histofine Simple Stain PO (M) Kit (Nichirei, Tokyo, Japan) according to the manufacturer's instructions. Chromogen 3,3-diaminobenzidine tetrahydrochloride was applied as a 0.02 % solution containing 0.005 % H_2O_2 in 50 mmol of ammonium acetate-citrate acid (pH 6.0). The sections then were lightly counterstained using Mayer's hematoxylin and mounted. Negative control sections were created by omitting the primary antibody, and no detectable staining was observed. Immunohistostaining results for all the samples were microscopically evaluated (×400) by two observers, and platelet aggregation was defined as CD42b-positive areas.

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria).[14] Significance was evaluated using Student's *t* test, analysis of variance, the Mann–Whitney *U* test, and Pearson's correlation coefficient. Survival curves were created using the Kaplan–Meier method and analyzed using the log-rank test. Prognostic factors were examined in uni- and multivariate analyses using a Cox proportional hazards model. Cutoff values for D-dimer, platelet, and PDM levels were evaluated using receiver operating characteristic curve analyses. All differences were considered significant at a P value lower than 0.05.

RESULTS

Associations of Postoperative Recurrence With D-Dimer, Platelet, and PDM Levels

The preoperative D-dimer levels were relatively high, with an average of 1.74 μg/mL (range, 0.2–9.6 μg/mL). The average preoperative platelet level was 238 × 104/μL (range, 99–571 × 104/μL). Compared with the no recurrence group, the recurrence group had significantly higher D-dimer levels ($P = 0.00075$*; Fig. 1a), exhibited a trend toward higher platelet levels ($P = 0.117$; Fig. 1b), and had significantly higher PDM levels ($P = 0.0000683$*; Fig. 1c). The optimal cutoff values were 1.3 μg/mL for D-dimer levels (area under the curve [AUC], 0.752; sensitivity, 0.846; specificity, 0.571; Fig. 1d), 245 × 104/μL for platelets (AUC, 0.624; sensitivity, 0.778; specificity,

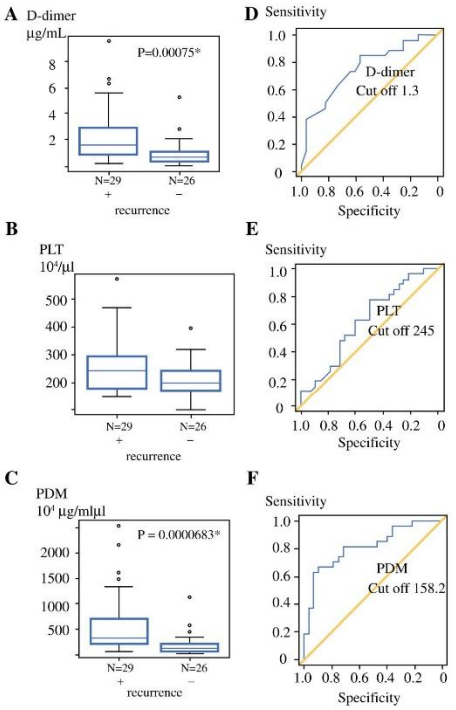

FIG. 1 The recurrence group exhibited significantly higher D-dimer ($P = 0.00075$) (**a**) and D-dimer platelet multiplication (PDM) ($P = 0.0000683$) levels (**c**). The high-platelet (PLT) groups exhibited a trend toward recurrence ($P = 0.117$) (**b**). The optimal cutoff values for D-dimer and PDM levels were determined using receiver operating characteristic curve analysis. The D-dimer cutoff value was 1.3 μg/mL (area under the curve [AUC], 0.752; sensitivity, 0.846; specificity, 0.571) (**d**). The platelet cutoff value was 245 × 104/μL (AUC, 0.624; sensitivity, 0.778; specificity, 0.5) (**e**). The PDM cutoff value was 158.2 × 104 μg/mL × μL (AUC, 0.813; sensitivity, 0.667; specificity, 0.893) (**f**). * $P < 0.05$

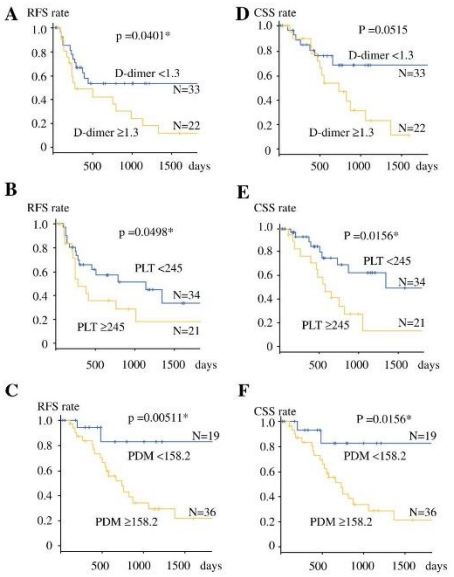

FIG. 2 The relationship between postoperative survival and D-dimer or D-dimer platelet multiplication (PDM) levels. Kaplan–Meier curves for the *low* and *high* groups are shown. **a** High D-dimer levels were associated with a poor recurrence-free survival (RFS) ($P = 0.0401$). **b** High PDM levels also were associated with a poor RFS ($P = 0.00511$). **c** High platelet levels were associated with a poor RFS ($P = 0.0498$). **d** High D-dimer levels tended to indicate a poor cancer-specific survival (CSS) ($P = 0.0515$). **e** High platelet levels were associated with a poor CSS ($P = 0.0156$). **f** High PDM levels also were associated with a poor CSS ($P = 0.0156$)

0.5; Fig. 1e), and 158.2 × 104 μg/mL × μL for PDM (AUC, 0.813; sensitivity, 0.667; specificity, 0.893; Fig. 1f). These cutoff values were used for the following analyses.

Correlations of Clinicopathologic Findings with D-Dimer, Platelet, and PDM Levels

The correlations of various clinicopathologic findings with D-dimer, platelet, and PDM levels are shown in Supplementary Table 2. None of these factors was significantly correlated with D-dimer or PDM levels. However, platelet levels were significantly correlated with tumor location ($P = 0.0243$*) and CA19-9 levels ($P = 0.0129$*) and exhibited a trend toward an association with hilar CC.

Predictive Values of D-Dimer, Platelet, and PDM Levels

The abilities of D-dimer and PDM levels to predict postoperative recurrence-free survival (RFS) and cancer-specific survival (CSS) are shown in Fig. 2. Compared with the low D-dimer group, the high D-dimer group exhibited poorer RFS ($P = 0.0428$*; Fig. 2a) and CSS ($P = 0.0515$; Fig. 2d). Compared with the low-platelet group, the high-platelet group had significantly poorer RFS ($P = 0.0498$; Fig. 2b) and CSS ($P = 0.0156$*; Fig. 2e). Compared with the low-PDM group, the high-PDM group had significantly poorer RFS ($P = 0.00511$*; Fig. 2c) and CSS ($P = 0.0156$*; Fig. 2f). The PDM levels exhibited a stronger correlation with CC prognosis than the D-dimer and platelet levels and predicted recurrence in both the

TABLE 1 Univariate and multivariate analysis of prognostic factors for recurrences using Cox proportional hazards model

Factor	Univariate analysis			Multivariate analysis		
	RR	95 % CI	*P* value	RR	95 % CI	*P* value
Age	5.553	1.472–24.5	0.00516*	8.330	1.69–41.0	0.00915*
Sex(M/F)	0.626	0.134–2.71	0.528	–	–	–
T stage(T1,2/3,4)	0.924	0.28–3.03	1	–	–	–
Lymphatic metastasis(∓)	1.07	0.327–3.51	1.000	–	–	–
Stage(I, II/III,IV)	2.127	0.565–8.67	0.245	–	–	–
Adjuvant theraphy(∓)	0.903	0.183–4.42	0.657	–	–	–
mGPS score (0/1,2)	5.804	1.288–37.12	0.0151*	5.550	0.976–31.5	0.0533
NLR (<3/≥3)	3.227	0.847–14.17	0.0797	–	–	–
PDM (<158.2/≥158.2)	14.2	3.39–59.2	0.000279*	9.570	1.88–48.7	0.00649*

* $P < 0.05$, *mGPS* modified glasgow prognostic score, *NLR* neutrophil/lymphocyte ratio, *RR* relativerisk, *95 % CI* 95 % confidence interval

univariate analysis (hazard ratio [HR], 14.2; 95 % confidence interval [CI], 3.39–59.2; $P = 0.000279$*) and the multivariate analysis (HR, 9.57; 95 % CI, 1.88–48.7; $P = 0.00649$*) (Table 1). None of the other clinicopathologic factors were significantly and independently associated with recurrence, and PDM provided a greater predictive value than age or mGPS. In addition, PDM was a predictive factor for CSS (HR, 5.021; 95 % CI, 1.173–21.49; $P = 0.02963$*).

Association of Inflammation With D-Dimer, Platelet, and PDM Levels

To examine the association of inflammation with D-dimer, platelet, and PDM levels, we evaluated several inflammation indexes such as C-reactive protein (CRP) levels, the neutrophil/lymphocyte ratio (NLR), and mGPS (score 0: CRP $\leq$ 1.0 mg/dL, score 1: CRP $>$ 1.0 mg/dL and albumin $\geq$ 3.5 g/dL, score 2: CRP $>$ 1.0 mg/dL and albumin $<$ 3.5 g/dL). The D-dimer levels were significantly correlated with NLR ($P = 0.0341$*; Fig. 3a) and mGPS ($P = 0.0000754$*; Fig. 3d). The PDM levels also were significantly correlated with NLR ($P = 0.00341$*; Fig. 3c) and mGPS ($P = 0.0000754$*; Fig. 3f). The platelet levels were correlated only with NLR ($P = 0.0171$*). The CRP levels were not significantly correlated with the D-dimer, platelet, or PDM levels.

CD42b Expression is Not Correlated with D-Dimer or Platelet Levels

To evaluate the relationship with local platelet aggregation, we investigated CD42b expression in the resected specimens because CD42b is a marker of platelet activation and aggregation that interacts with the extracellular matrix and adhesion molecules. The expression of CD42b was not significantly correlated with the D-dimer ($P = 0.824$) or platelet ($P = 1$) levels (Fig. 4).

DISCUSSION

The current study found that D-dimer levels of 1.3 μg/mL or higher, platelet levels of 245 × 104/μL or higher, and PDM levels of 158.2 × 104 μg/mL*μL or higher were associated with postoperative recurrence and a poor prognosis for patients with primary CC. Moreover, PDM levels were more strongly associated with recurrence and prognosis than D-dimer and platelet levels, indicating that PDM levels might be a clinically useful prognostic marker for CC. In this context, Zacharski et al.[15] have reported that cancer cells promote coagulation by inactivating the fibrinolytic system (e.g., via urokinase-type plasminogen activator) and that many coagulation mechanisms may contribute to each type of carcinoma. Caine et al.[12] also have reported that breast and prostate cancers were associated with elevated levels of coagulation factors (e.g., D-dimer, fibrinogen, interleulin-6, soluble P-selectin, and vascular endothelial growth factor). Thus, cancer cells appear to activate coagulation.

In the current study, high D-dimer and PDM levels were correlated with poor RFS and CSS among patients with primary CC, and high PDM levels were an independent prognostic factor for recurrence in the multivariate analyses. Furthermore, several previous reports have shown that D-dimer levels are associated with recurrence or a poor prognosis in colorectal cancer [10,11] gastric cancer,[9] prostate cancer,[8] lung cancer,[6,7] renal cancer,[16] ovarian cancer,[17] and cervical carcinoma. These findings agree with our findings from the current study. Therefore, D-dimer and PDM levels may help to predict prognosis in cases of CC, although PDM levels were a more significant predictor than D-dimer levels alone. Moreover, we found relatively

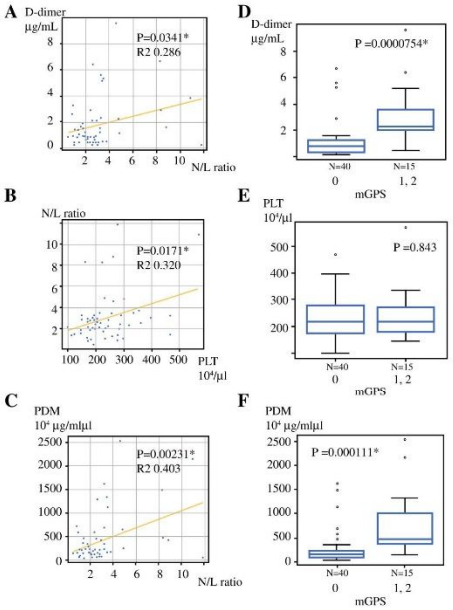

FIG. 3 The correlations of D-dimer levels with the neutrophil/lymphocyte ratio (NLR) ($P = 0.00341$) (**a**) and modified Glasgow Prognostic Score (mGPS) ($P = 0.0000754$) (**d**). Platelet levels were correlated with NLR ($P = 0.0171$) (**b**) but not with mGPS ($P = 0.843$) (**f**). D-dimer platelet multiplication levels were correlated with NLR ($P = 0.00341$) (**c**) and mGPS ($P = 0.0000754$) (**f**). * $P < 0.05$

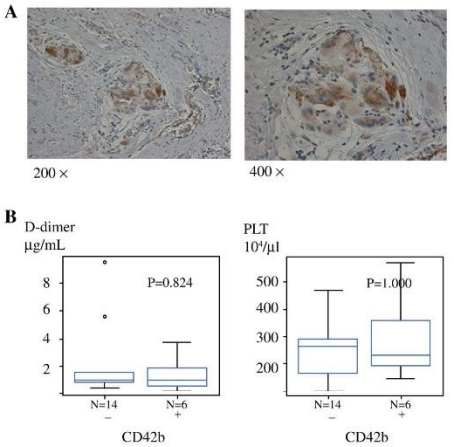

FIG. 4 Immunohistochemical staining of CD42b in primary cholangiocarcinoma specimens. **a** Positive CD42b expression (×200, ×400). **b** Positive CD42b expression was not significantly correlated with D-dimer ($P = 0.824$) or platelet ($P = 1$) levels. * $P < 0.05$

high D-dimer levels (average, 8.74 μg/mL) in cases of recurrence, indicating that D-dimer levels reflected the likelihood of tumor recurrence.

Several previous reports have evaluated the relationship between cancer and inflammation,[18,19] which may be relevant in cases of cholangitis because cholangitis is frequently complicated by CC. In the current study, D-dimer and PDM levels were significantly correlated with NLR and mGPS (inflammation indexes). In this context, neutrophils produce ligands and cytokines and promote tumor progression and metastasis.[20] However, lymphocytes typically exert an antitumor effect, and the presence of fewer lymphocytes can reduce this antitumor effect.[21] Therefore, the NLR reflects the balance between tumor progression and immune suppression and is related to tumor prognosis.

Several reports also have shown that NLR is associated with recurrence or a poor prognosis in colorectal cancer,[22] gastric cancer,[23] pancreatic cancer,[24] and lung cancer.[25] Moreover, mGPS is an index of inflammation associated with prognosis in cases of hilar CC,[13] breast cancer, prostate cancer, and lung cancer.[26] The current study found that D-dimer, platelet, and PDM levels were correlated with NLR and mGPS, indicating that these markers may reflect a systemic inflammatory state.

We also investigated the association of D-dimer levels with local platelet aggregation. In this context, CD42b is a platelet surface marker that binds to von Willebrand factor, and anti-CD42b antibodies can be used to identify platelets during immunohistochemistry.[27] However, no previous reports have described CD42b and cancer prognosis, and we did not observe any significant correlation of platelet aggregation with D-dimer or platelet levels. Thus, it appears that D-dimer and platelet levels are more strongly correlated with systemic inflammation than with local platelet aggregation.

Our study provides the first evidence that PDM levels may be a novel biomarker for prognosis in cases of CC. In this context, PDM reflects the systemic inflammatory state in relation to NLR and mGPS rather than local coagulation, and this systemic inflammation is a relevant factor that affects CC progression. Therefore, PDM could be an effective prognostic factor for CC. However, it is unclear how tumor progression is mechanistically related to D-dimer and platelet levels. Therefore, further prospective studies are needed to evaluate this mechanism.

In conclusion, we found that high D-dimer, platelet, and PDM levels were associated with poor RFS and CSS for patients with CC. Furthermore, PDM levels exhibited the

strongest correlation with these outcomes. Therefore, PDM levels may be a useful biomarker for recurrence and prognosis in cases of CC, and our findings suggest that platelets or coagulation factors may be a promising target for controlling cancer progression.

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DISCLOSURE There are no conflicts of interest.

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