

Inflammation-based prognostic score is a useful predictor of postoperative outcome in patients with extrahepatic cholangiocarcinoma

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journal or publication title	Journal of hepato-biliary-pancreatic sciences
volume	20
number	3
page range	389-395
year	2013-03
権利	(C) Japanese Society of Hepato-Biliary-Pancreatic Surgery and Springer 2012. The original publication is available at www.springerlink.com .
URL	http://hdl.handle.net/2241/00122564

doi: 10.1007/s00534-012-0550-6

1 ORIGINAL ARTICLE

2 **Inflammation-based prognostic score is a useful predictor of postoperative outcome in**
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24 Key words: Glasgow prognostic score, C-reactive protein, albumin, systemic inflammatory

- 1 response, extrahepatic cholangiocarcinoma
- 2 Word Count: 3702. Number of Figures: 3. Number of Tables: 4.
- 3

1 **Abstract**

2 *Background/purpose:* Recent studies have revealed that the Glasgow prognostic score
3 (GPS), an inflammation-based prognostic score, is useful for predicting outcome in a
4 variety of cancers. This study sought to investigate the significance of GPS for
5 prognostication of patients who underwent surgery with extrahepatic cholangiocarcinoma.
6 *Methods:* We retrospectively analyzed a total of 62 patients who underwent resection for
7 extrahepatic cholangiocarcinoma. In 62 patients we calculated the GPS as follows: Patients
8 with both an elevated C-reactive protein (CRP) (>10 mg/L) and hypoalbuminemia (<35
9 g/L) were allocated a score of 2. Patients with either one or none of these abnormalities
10 were allocated a score of 1 or 0, respectively. Prognostic significance was analyzed by the
11 log-rank test and a Cox proportional hazards model.
12 *Results:* Overall survival rate was 25.5% at five years for all 62 patients. Venous invasion
13 ($p=0.01$), pathological primary tumor (pT) category ($p=0.013$), lymph node metastasis (pN)
14 category ($p<0.001$), TNM-stage ($p<0.001$), and GPS ($p=0.008$) were significantly
15 associated with survival by univariate analysis. A Cox model demonstrated that increased
16 GPS was an independent predictive factor with poor prognosis.
17 *Conclusions:* The preoperative GPS is a useful predictor of postoperative outcome in
18 patients with extrahepatic cholangiocarcinoma.

19

1 **Introduction**

2 Of all gastrointestinal malignancies, pancreatobiliary carcinomas continue to have poor
3 survival rates.¹⁻¹² Multiple studies have examined potential prognostic factors in patients
4 undergoing resection for extrahepatic cholangiocarcinoma, including the presence of lymph
5 node metastases,^{2,3,5,6,8-12} the number of lymph node metastases,^{11,12} resection margin,^{1,3,5-9}
6 tumor differentiation,^{1,9} and depth of invasion.^{7,12} There is increasing evidence that the GPS,
7 a score based on the systemic inflammatory response (SIR) that evaluates CRP and albumin
8 serum levels, is a useful scoring system to determine the prognosis of patients with
9 advanced cancers.¹³⁻¹⁵ The SIR encompasses the infiltration of proinflammatory
10 lymphocytes, which produce cytokines and chemokines within the tumor
11 microenvironment, predisposing the tumor to further progression, invasion, and
12 metastases.¹⁶ A state of chronic inflammation is thought to play a key role in the initiation,
13 promotion, and progression of malignant diseases.¹⁷

14 To our knowledge, the GPS has not been investigated in patients with extrahepatic
15 cholangiocarcinoma. This study sought to examine the relationship between an
16 inflammation-based prognostic score, Glasgow prognostic score (GPS), and survival in
17 patients undergoing resection for extrahepatic cholangiocarcinoma. In addition, we
18 evaluated the relative prognostic power of the GPS in comparison to other
19 clinicopathologic factors after surgical resection.

20

1 **Patients and Methods**

2 This study retrospectively analyzed 62 consecutive patients (41 men and 21 women)
3 with extrahepatic cholangiocarcinoma who underwent surgical resection at Tsukuba
4 University Hospital between January 2001 and December 2009. Mean patient age was 69.0
5 years (range; 34 to 88 years). The mean value of preoperative serum total bilirubin level
6 was 7.1 ± 6.9 mg/dl and 36 patients (58%) had preoperative biliary drainage due to
7 obstructive jaundice (Table 1). The appropriate biliary drainage procedures were performed
8 in the 36 patients. Twenty-four patients underwent percutaneous transhepatic biliary
9 drainage (PTBD), 10 patients underwent endoscopic nasogastric biliary drainage (ENBD),
10 and 2 patients underwent endoscopic retrograde biliary drainage (ERBD).

11 The predominant sites of the primary tumor were the hilar bile duct in 17 patients (27%),
12 proximal bile duct in 15 patients (24%), middle bile duct in 12 patients (19%), and distal
13 bile duct in 18 patients (30%). The appropriate surgical procedures depended on the
14 location of the primary tumor. Twenty-five patients underwent hepatectomy with
15 extrahepatic bile duct resection (Hx), 24 patients underwent a pancreaticoduodenectomy
16 (PD) or subtotal stomach-preserving pancreaticoduodenectomy (SSPPD), 11 patients
17 underwent extrahepatic bile duct resection (EBDR), and 2 patients underwent a combined
18 hepatectomy and pancreaticoduodenectomy (HPD) (Table 1). Systemic regional
19 lymphadenectomy, which involved resection of the lymph nodes in the hepatoduodenal
20 ligament, posterior pancreatoduodenal nodes, and along the common hepatic artery, was
21 performed in all patients.

22 After surgical resection, we opened the extrahepatic bile duct longitudinally. Specimens
23 were fixed in 10% formalin for several days, and then serially sectioned at 5-mm intervals.
24 Specimens were prepared in the standard manner for microscopic examination by

1 hematoxylin and eosin staining. Histopathological findings were described in accordance
2 with the tumor-node-metastasis (TNM) staging of the American Joint Committee on Cancer
3 (AJCC) as well as the General rules for Surgical and Pathological Studies on Cancer of the
4 Biliary Tract of the Japanese Society of Biliary Surgery (JSBS).^{18,19} Primary tumor status,
5 lymph node category, and histopathological tumor grade were classified according to the
6 AJCC-TNM classification system. We examined the histopathological factors of lymphatic
7 invasion, venous, and perineural invasion and recorded our findings in accordance with
8 JSBS guidelines.

9 In the patients who underwent the biliary drainage procedures, we diagnosed whether
10 they had cholangitis or not according to systemic inflammatory response syndrome (SIRS)
11 criteria; including fever, abnormal white blood cell count, tachypnea, and tachycardia, as
12 well as filthy colored bile juice which is suspect of bile contamination. Blood samples were
13 always taken from the patients within one week before surgery in order to confirm there
14 were no other problems or abnormality in the patients prior to receiving anesthesia and
15 surgery. We used the blood sample data at that time; i.e., serum CRP and albumin for the
16 GPS system. In the present study, we used the blood sample data for the GPS system in
17 accordance with the above mentioned way by which we had diagnosed no cholangitis. We
18 routinely investigated bacterial culture of the drained sample bile juice in the patients who
19 underwent the biliary drainage procedures. In the culture of the bile juice in 36 patients who
20 underwent the biliary drainage procedures, we confirmed negative pathogenic bacteria in
21 15 patients and normal bacterial flora in 15 patients. Data was not found in the other 6
22 patients. It is said that after the biliary drainage procedures, secondary exogenous
23 contamination of bile juice occurs in most patients²⁰, so we always use antibiotics for 2-3
24 days just after the drainage procedures. In fact, only 4 of 36 patients had fever after the

1 biliary drainage procedures and their fever went down soon, and the serum bilirubin level
2 decreased gradually in all patients. After we confirmed that the patients had no cholangitis,
3 they underwent surgical resection 31.1 (mean, range; 6-88) days after the biliary drainage
4 procedures. The coefficient of variation for these methods, over the range of measurement,
5 was less than 5%, as established by routine quality control procedures.

6 Briefly, patients with both an elevated CRP level (>10 mg/L) and hypoalbuminemia
7 (<35 g/L) were allocated a score of 2, while patients with only one of these biochemical
8 abnormalities were allocated a score of 1. Patients with neither of these abnormalities were
9 allocated a score of 0, as described previously.¹³⁻¹⁵

10 Patients were followed regularly in outpatient clinics every 1-6 months. Follow-up
11 information for all 62 patients was obtained from records of routine clinic appointments and
12 telephone calls to the patients and their referring physicians. Sites of disease recurrence
13 were determined from imaging studies including computed tomography (CT) and magnetic
14 resonance imaging (MRI).

15 Survival curves were calculated using the Kaplan-Meier method.²¹ Differences between
16 curves were evaluated using the log-rank test. P values < 0.05 were considered statistically
17 significant. We used a multivariate Cox proportional hazard model to determine if factors
18 independently affected postoperative survival.²² Correlations between GPS classification
19 and age, predominant location, histological grade, venous invasion, pathological primary
20 tumor (pT) category, lymph node metastasis, and TNM-stage were analyzed by the χ^2 test or
21 Fisher exact test as appropriate. Statistical analyses were performed using a statistical
22 analysis software package (StatView version 5.0 Abacus Concepts, Inc., Berkeley, CA).

23

1 **Results**

2 A GPS of 0, 1, and 2 were assigned to 32, 20, and 10 patients, respectively. There were
3 no significant differences in tumor characteristics of extrahepatic cholangiocarcinoma such
4 as age, predominant location, histologic grade, venous invasion, pathological primary
5 tumor (pT) category, lymph node metastasis, TNM-stage, carbohydrate antigen 19-9
6 (CA19-9), and carcinoembryonic antigen (CEA) across the different GPS groups (Table 2).

7 At last follow-up, 36 patients had died of tumor recurrence, while five patients had died
8 of other causes without evidence of tumor recurrence. Two patients were alive with
9 metastases and the other remaining 19 patients were alive without evidence of disease. One
10 patient died within 30 days of surgical resection, and two patients died in the hospital,
11 yielding a surgical mortality rate of 4.8%. Overall survival rates were 37.3% at three years
12 and 25.5% at five years for all 62 patients. Venous invasion, pathological primary tumor
13 (pT) category, lymph node metastasis (pN) category, TNM-stage, and GPS were found to
14 be significant prognostic factors by univariate analysis (Table 3). In contrast, age, gender,
15 predominant location, operative time, intraoperative bleeding, histological grade, lymphatic
16 invasion, perineural invasion, surgical margin, CA19-9, and CEA were not found to be
17 significant predictors of survival.

18 Kaplan-Meier analysis demonstrated significant differences in survival among the GPS
19 groups of 2 (mean survival, 12.7 months; 95%CI, 7.8-17.6 months), 1 (mean survival, 37.2
20 months; 95%CI, 20.0-54.4 months), and 0 (mean survival, 34.1 months; 95%CI, 24.9-43.3
21 months) ($p=0.008$) (Figure 1). Although there was significant difference between the GPS
22 of 1 and the GPS of 2 ($p=0.031$), no significant difference was seen between the GPS of 0
23 and the GPS of 1 ($p=0.866$). Considering the results of Figure 1, we aggregated the
24 categories “GPS of 0” and “GPS of 1” into one category (“GPS of 0-1”) (Figure 2).

1 Kaplan-Meier analysis also demonstrated a significant difference between the GPS of 2
2 (mean survival, 12.7 months; 95%CI, 7.8-17.6 months) and the GPS of 0-1 (mean survival,
3 34.9months; 95%CI, 26.5-43.3 months) ($p=0.002$) (Figure 2). Thirty-six patients without
4 lymph node metastases had a five-year survival of 44.2% in comparison to a five-year
5 survival of 0% for 26 patients with lymph node metastases ($P<0.001$) (Figure 3). A
6 multivariate analysis with a Cox proportional hazards model, utilizing venous invasion,
7 pathological primary tumor (pT) category, lymph node metastasis (pN) category, and GPS,
8 revealed that a GPS of 2 was an independent predictive factor of survival (HR=2.787,
9 $p=0.022$) (Table 4). TNM-stage, pT, and pN factors are considered to have a strong
10 correlation because pT and pN are components of TNM-stage. In fact, in our multivariate
11 analysis, analysis including these three factors was not able to show estimators because of
12 multicollinearity (data not shown). Therefore, we excluded TNM-stage from the
13 multivariate analysis and adopted pT and pN, which are medically essential and impressive,
14 to obtain medically meaningful results.

15

1 Discussion

2 McMillan and coworkers^{13-15, 23-26} demonstrated that GPS is a useful predictor of
3 postoperative death for multiple cancers including non small-cell lung¹³, breast¹⁴,
4 gastro-esophageal^{15, 23}, pancreatic²⁴, renal²⁵, and colorectal²⁶ cancers. The cases in these
5 studies, however, were typically inoperable or metastatic. Recently, several reports have
6 investigated GPS in patients with operable primary colorectal cancers.^{16, 27-30} As yet, no
7 reports have addressed the association between GPS and survival in extrahepatic
8 cholangiocarcinoma. To our knowledge, this is the first report evaluating the use of GPS in
9 patients undergoing resection for extrahepatic cholangiocarcinoma.

10 In this study, a Cox proportional hazards model revealed that a GPS of 2 was an
11 independent predictive factor of survival (Table 4). This data suggests that GPS is a
12 prognostic factor of outcome; higher GPS portends poor tumor biology and worse survival.
13 On the other hand, a Cox proportional hazards model revealed that lymph node metastasis
14 had a marginal significance for survival (HR=2.066, $p=0.071$) (Table 4). Numerous studies
15 have demonstrated that lymph node metastasis is the most accurate prognostic factor used
16 for pancreatobiliary carcinoma; patients with lymph node metastases have a significantly
17 worse survival than patients with node-negative disease. Jang et al. and Sasaki et al.
18 reported that lymph node metastasis is a significant factor affecting patient outcome after
19 surgery^{3, 11}.

20 A wide range of systemic inflammatory responses results from infection, tissue injury,
21 immunological disorders, and cancer. C-reactive protein (CRP) is an acute-phase protein
22 produced by liver. The liver is central to the elaboration of the systemic inflammatory
23 response. Cytokines such as interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis
24 factor α (TNF- α) stimulate hepatocytes to synthesize and release into the systemic

1 circulation a variety of acute-phase proteins, such as CRP, which initiate and sustain the
2 systemic inflammatory response. ^{16,31} McMillan et al. demonstrated that CRP
3 concentrations were independently associated with overall survival in patients who
4 underwent potentially curative resection for colorectal cancer.³²

5 In the past, hypoalbuminemia in cancer patients was thought to result from nutritional
6 depletion secondary to the tumor. However, it has been postulated that reduction in albumin
7 concentrations is secondary to the presence of the systemic inflammatory response.²⁹ The
8 acute phase protein response (APPR) is characterized by lower serum concentrations of
9 several serum proteins, such as albumin and transferrin, which results from both decreased
10 synthesis and altered distribution. Serum concentration of CRP and immunoglobulins
11 increase due to increased synthesis.^{33,34} In patients with cancer, there is evidence that the
12 stereotypical APPR, with an increase in CRP and decreased albumin, occurs across a wide
13 range of different tumor types.³¹ Therefore, albumin levels may not only reflect underlying
14 nutritional status, but also the presence of comorbidities.²⁹

15 The relationship between the systemic inflammatory response (GPS) and decreased
16 survival in patients with extrahepatic cholangiocarcinoma is not clear and is likely to be
17 complex. Ishizuka et al. ¹⁶ commented that cancer promotes the release of proinflammatory
18 cytokines, leading in extreme cases to cachexia and malnutrition. Crozier et al. ²⁹ suggested
19 that an elevated GPS may reflect compromised cell-mediated immunity as an elevated CRP
20 and hypoalbuminemia are associated with lymphocytopenia and an impaired T-lymphocytic
21 response within tumors. Elevated CRP concentrations and hypoalbuminemia have also
22 been shown to be associated with an up-regulation of the components of an innate immune
23 system, including complement and macrophage activity. These results suggest that immune
24 function is compromised prior to surgery, resulting in faster disease progression and

1 decreased long-term survival. There has been no clear basis of the relationship between a
2 high GPS prior to surgery and poor survival in various cancers. However, based on the
3 previous reports^{16,29}, we could speculate that there might be a kind of extrahepatic
4 cholangiocarcinoma that produces or promotes cytokines such as IL-6 and TNF- α .
5 Therefore, SIR induced by the cytokine causes the impaired immunity in patients, resulting
6 in fast progression of the carcinoma and decreased survival. Furthermore, because there
7 was a marginal significant difference in lymph node metastasis across the different GPS
8 groups ($P=0.059$), a high GPS might have the characteristic of having a high tendency for
9 lymphatic spread of the extrahepatic cholangiocarcinoma.

10 Many previously reported prognostic factors have been evaluated only after surgery,
11 because these were pathological factors. In contrast, GPS can easily be calculated from the
12 serum CRP and albumin levels prior to surgery. Due to lower costs and improved
13 convenience, preoperative GPS is a useful system to assess postoperative survival in
14 patients with extrahepatic cholangiocarcinoma.

15 Several limitations of this study, however, need to be addressed. This study had a
16 retrospective design and was limited by a small number of patients. In addition, there is a
17 possibility that the heterogeneity of the primary tumor location or the surgical procedures
18 affected the results of this study. These results will need to be confirmed by a
19 multi-institutional cohort of patients.

20 GPS should be routinely used for patients with extrahepatic cholangiocarcinoma, as it
21 can help stratify those patients who need additional treatment. Use of this classification
22 system in the analysis of future clinical trials investigating extrahepatic cholangiocarcinoma
23 will also help determine appropriate treatments according to disease severity.

24

1 **Conclusions**

2 In conclusion, preoperative GPS is a promising predictor of postoperative outcomes in
3 patients with extrahepatic cholangiocarcinoma.

4

5 **Conflict of interest statement:** No conflict of interest

6

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2

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- 6

1 **FIGURE LEGENDS**

2 **Fig. 1**

3 Survival curves stratified by Glasgow prognostic score (GPS) 0, 1, and 2.

4 There was a statistically significant difference among the three groups (five-year survival
5 rates: GPS of 0, 26.8%; GPS of 1, 42.6%; GPS of 2, 0%) ($p=0.008$). While there was a
6 significant difference between the GPS of 1 and the GPS of 2 ($p=0.031$), there was no
7 significant difference between the GPS of 0 and the GPS of 1 ($p=0.866$).

8

9 **Fig. 2**

10 Survival curves stratified by Glasgow prognostic score (GPS) 0-1 and 2.

11 There was a statistically significant difference between the GPS of 0-1 and the GPS of 2
12 ($p=0.002$).

13

14 **Fig. 3**

15 Survival curves stratified by lymph node status.

16 There was a statistically significant difference in survival between patients with positive
17 lymph nodes and those with negative nodes ($p<0.001$).

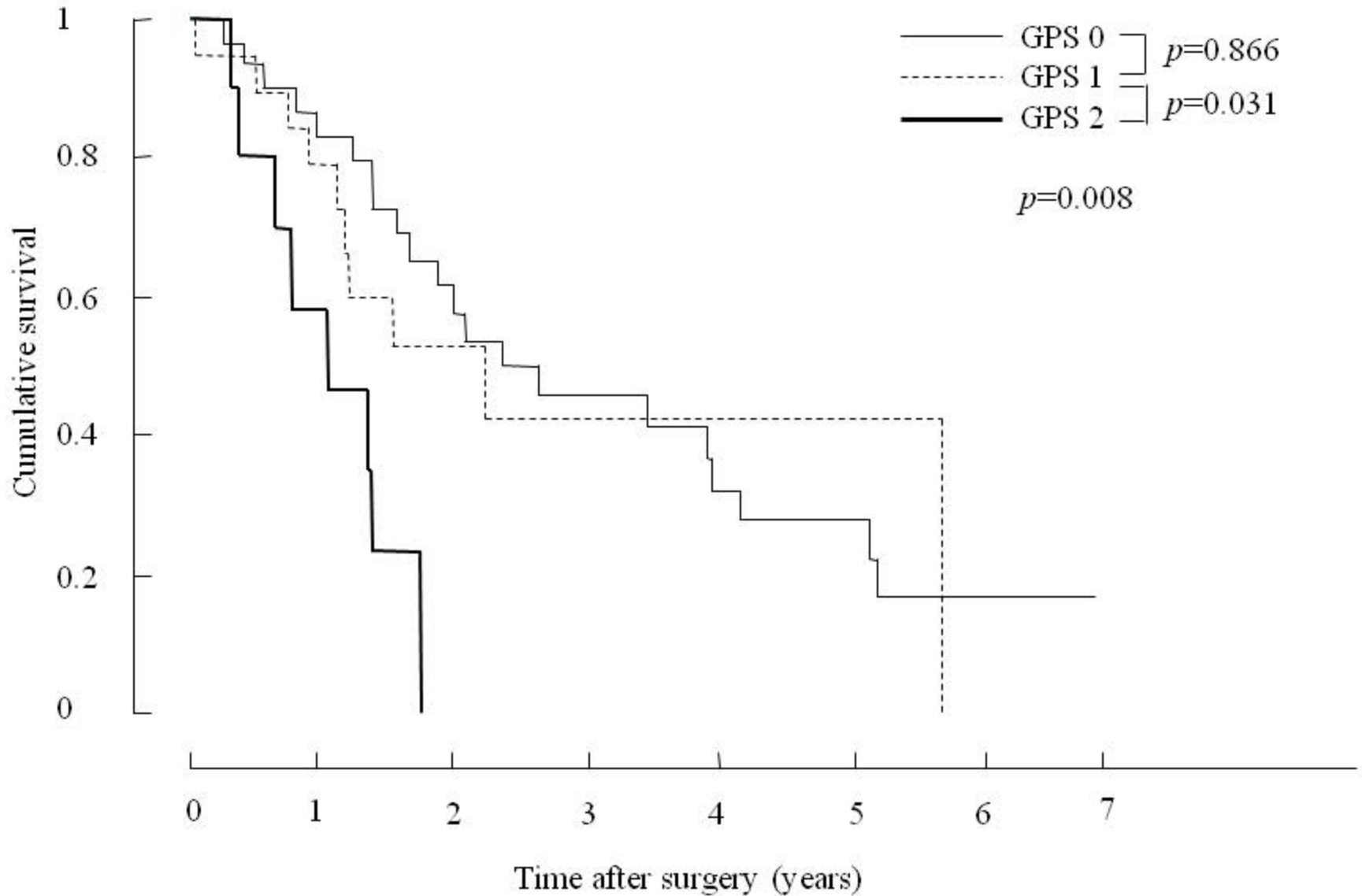


Fig. 1

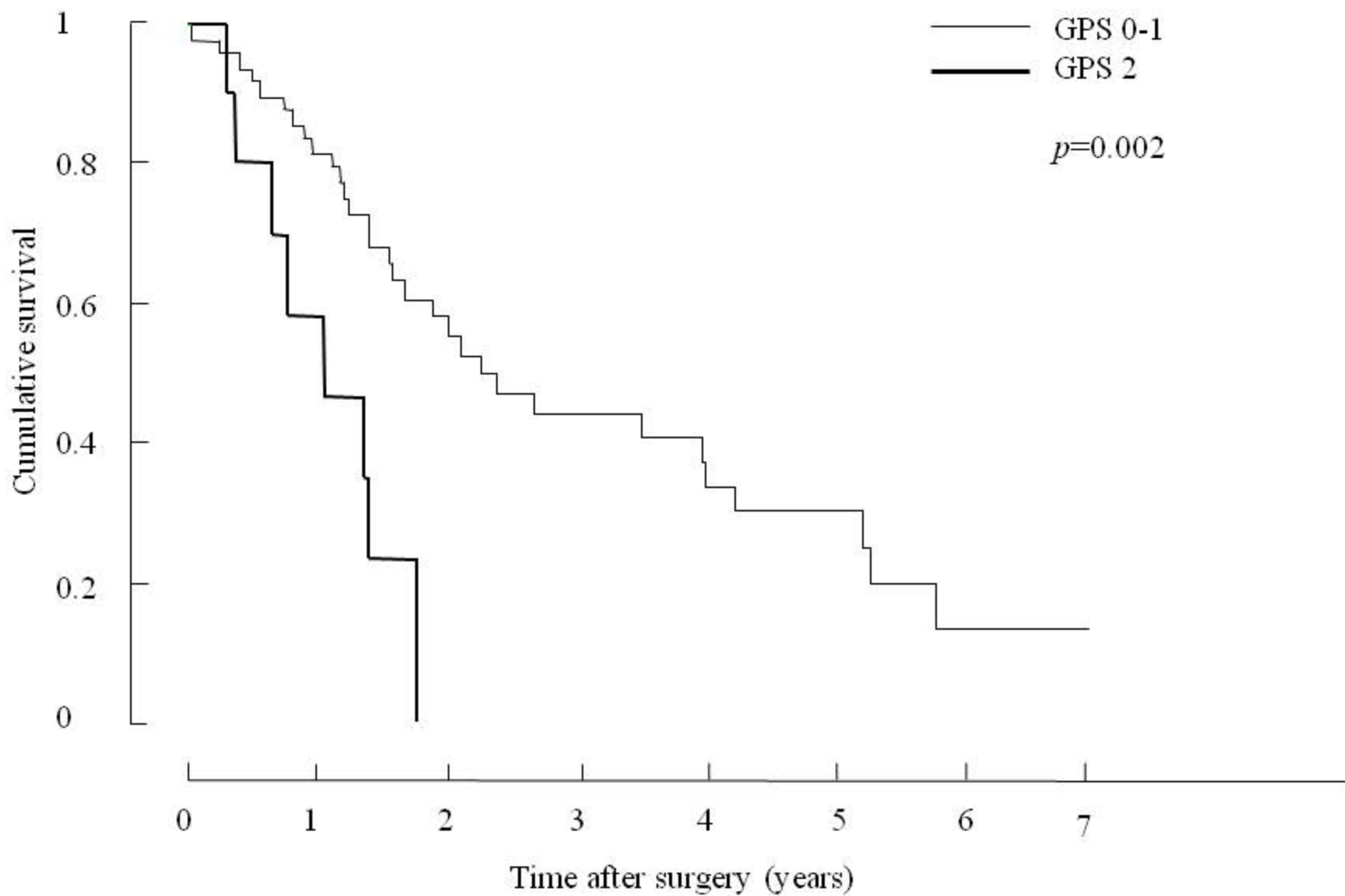


Fig. 2

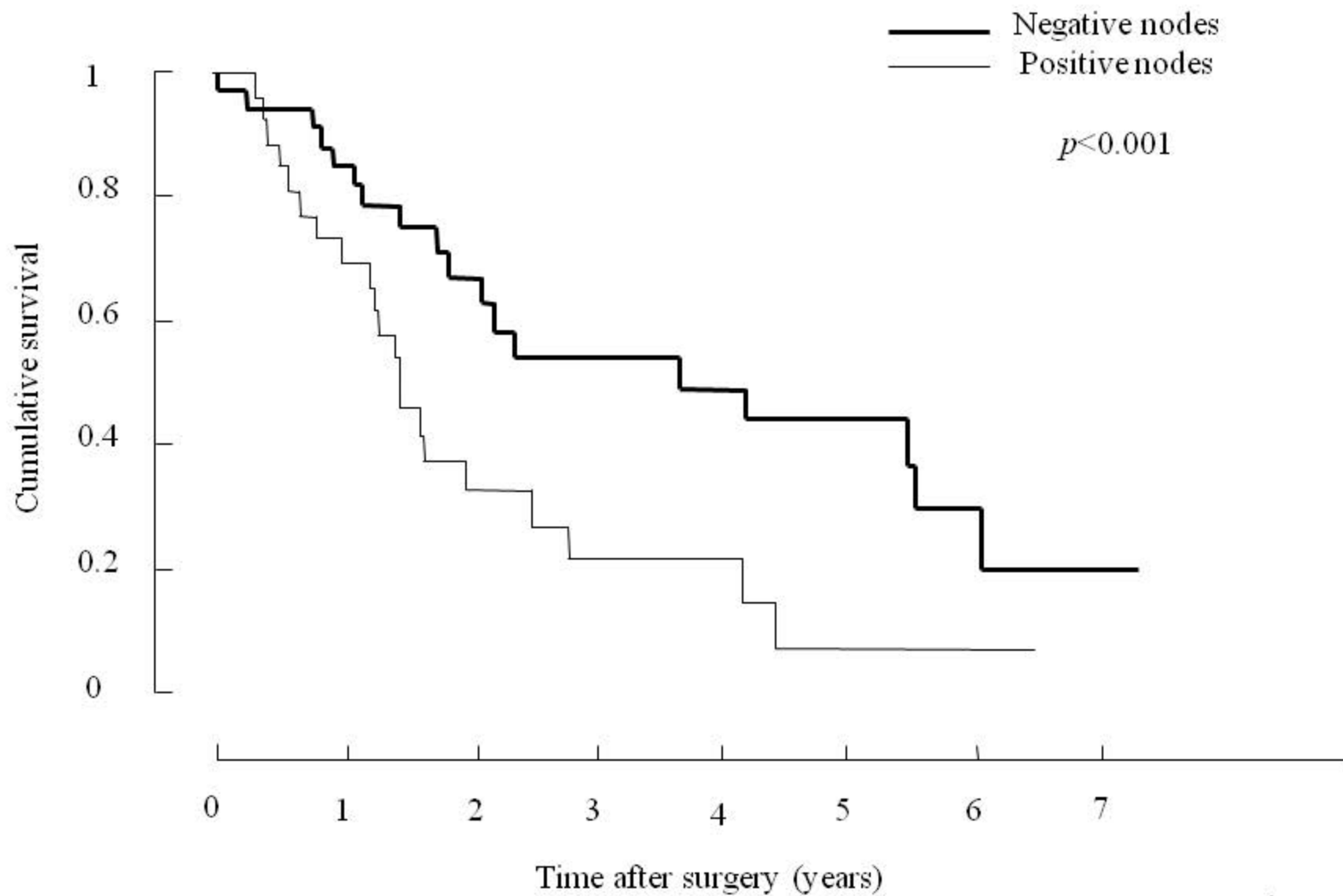


Fig. 3

Table 1. Clinical and morphological features of patients

Variable	Number of patients (%)
Age (year) (mean, range)	69.0 (34-88)
Gender	
Male (n, %)	41 (66)
Female (n, %)	21 (34)
Preoperative serum total bilirubin level (mg/dL) (mean, range)	7.1 (0.4-22)
Preoperative biliary drainage (yes/no)	36/26
<u>PTBD</u>	<u>24(39)</u>
<u>ENBD</u>	<u>10(16)</u>
<u>ERBD</u>	<u>2(3)</u>
Site (n, %)	
Hilar	17 (27)
proximal	15 (24)
middle	12 (19)
distal	18 (30)
Surgery (n, %)	
Hx	25 (40)
PD, SSPPD	24 (39)
EBDR	11 (18)
HPD	2 (3)
TNM stage (n, %)	
0	5 (8)
IA	9 (15)
IB	7 (11)
IIA	13 (21)
IIB	15 (24)
III	11 (18)
IV	2 (3)
GPS (n, %)	
0	32 (50)
1	20 (34)
2	10 (16)

PTBD, Percutaneous transhepatic biliary drainage; ENBD, endoscopic nasogastric biliary drainage; ERBD, endoscopic retrograde biliary drainage; Hx, Hepatectomy combined with extrahepatic bile duct resection; PD, Pancreaticoduodenectomy SSPPD, Subtotal stomach-preserving pancreaticoduodenectomy; EBDR, Extrahepatic bile duct resection; HPD, Hepatectomy combined with pancreaticoduodenectomy; GPS, Glasgow prognostic score

Table 2. Relationships between tumor characteristics of extrahepatic cholangiocarcinoma and GPS

Variables	GPS 0	GPS 1	GPS 2	<i>P-value</i>
Age (year)				0.874
<70	17	10	6	
≥70	15	10	4	
Predominant location				0.291
Hilar/proximal	17	8	7	
Middle/distal	15	12	3	
Histological grade				0.538
Well/moderately	27	15	7	
Poor	5	5	3	
Venous permeation				0.668
Negative	21	12	5	
Positive	11	8	5	
T stage				0.781
Tis	4	1	0	
T1	6	2	2	
T2	8	3	2	
T3	10	10	4	
T4	4	4	2	
Lymph node metastasis				0.059
Negative	18	15	3	
Positive	14	5	7	
TNM stage				0.14
0	4	1	0	
IA	5	2	2	
IB	5	2	0	
IIA	4	8	1	
IIB	9	2	4	
III	5	4	2	
IV	0	1	1	
CA19-9 (U/ml)				0.419
Normal	9	6	5	
High	23	14	5	
CEA (ng/ml)				0.405
Normal	22	15	9	
High	10	5	1	

Table 3. Prognostic factors by a univariate analysis

Factor	Number of Patients	3-year rate (%)	5-year rate (%)	<i>P</i> -value
All	62	37.3	25.5	
Age (year)				0.211
<70	31	43.4	29.7	
≥70	31	32.4	21.6	
Gender				0.408
Male	41	39.2	27.5	
Female	21	33.6	22.4	
Predominant location				0.053
Hilar/proximal	32	23.9	19.1	
Middle/distal	30	51.4	32.1	
Operation Time (minutes)				0.584
<600	32	37.5	25.0	
≥600	30	29.1	29.1	
Intraoperative bleeding				0.084
<1300	37	47.0	29.9	
≥1300	25	17.0	17.0	
Histological grade				0.838
Well/moderately	49	37.5	21.9	
Poor	13	40.2	40.2	
Tumor invasion				
Lymphatic invasion				0.197
Negative	21	54.4	43.5	
Positive	41	30.2	18.9	
Venous invasion				0.01
Negative	38	48.9	36.2	
Positive	24	16.6	0	
Perineural invasion				0.29
Negative	10	56.3	28.1	
Positive	52	33.9	24.3	
T stage				0.013
Tis	5	80.0	60.0	
T1	10	40.0	40.0	
T2	13	48.5	32.3	
T3	24	35.2	21.1	
T4	10	0	0	
Lymph node metastasis				<0.001
Negative	36	54.0	44.2	
Positive	26	16.9	0	
TNM stage				<0.001
0	5	80.0	80.0	
IA	9	38.1	38.1	
IB	7	47.6	47.6	
IIA	13	67.9	40.7	
IIB	15	22.2	0	
III	11	0	0	
IV	2	0	0	
Surgical margin				0.081
Negative	36	43.1	31.5	
Positive	26	29.9	17.9	
CA19-9				0.595
Normal	20	49.0	32.6	
High	42	33.9	23.3	
CEA				0.461
Normal	46	32.9	20.6	
High	16	46.8	37.4	
GPS				0.008
0	32	44.6	26.8	
1	20	42.6	42.6	
2	10	0	0	

Table 4. Multivariate analysis for survival

Parameter	HR	95% CI	<i>P-Value</i>
Venous invasion : positive	1.237	0.561 – 2.727	0.598
T stage : T3,4	1.817	0.884 – 3.736	0.104
Lymph node metastasis : positive	2.066	0.938 – 4.549	0.071
GPS : 2	2.787	1.153 – 6.735	0.022

GPS, Glasgow prognostic score; HR, hazard ratio; CI, confidence interval