OPEN ACCESS

Saudi Journal of Medicine

Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) | ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Measurement of Serum Procalcitonin as an Early Predictor of Post-operative Complications after Elective Liver Resection

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DOI: https://doi.org/10.36348/sjm.2025.v10i07.008 | **Received:** 18.04.2025 | **Accepted:** 24.05.2025 | **Published:** 30.07.2025

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Abstract

Background: Accurate and early detection of postoperative complications after elective liver resection (LR) remains a challenge. A reliable predictor is essential for guiding therapy and improving outcomes. This study aimed to evaluate the role of serum procalcitonin (PCT) in predicting postoperative complications after LR. ***Methods:*** This prospective observational study was conducted at BSMMU, Dhaka, from July 2021 to June 2024. A total of 84 patients undergoing elective LR were included. Informed consent was obtained before surgery. Serum PCT levels were measured on postoperative days (POD) 1, 3, and 7 using the Siemens Atellica IM BRAHMS PCT analyzer. Other markers, including WBC count, CRP, and liver and renal function tests, were also recorded. Patients were categorized into two groups: those without complications (group 1, n=20) and those with complications (group 2, n=22). Statistical analyses were conducted using SPSS 25.0, with a significance level of $P<0.05$. ***Results:*** Postoperative complications occurred in 52.4% of patients. Mean serum PCT levels were significantly higher in group 2 than in group 1 on POD 1 (0.898 ± 0.787 vs. 2.508 ± 2.587 µg/L, P=0.011), POD 3 (0.314 ± 0.249 vs. 0.890 ± 0.735 µg/L, P=0.002), and POD 7 (0.181 ± 0.217 vs. 0.611 ± 0.610 µg/L, P=0.005). WBC count and CRP levels did not show statistical significance. ROC analysis identified a PCT cutoff of 1.100 µg/L on POD 1, with sensitivity 86.4%, specificity 70.0%, PPV 74.2%, and NPV 83.7%. ***Conclusion:*** Serum PCT on POD 1 is a strong early predictor of complications after elective LR. A cutoff value of 1.100 µg/L accurately predicts morbidities, regardless of the type of disease or surgical procedure.

Keywords: Liver Resection, Procalcitonin, Early Prediction, Outcome, Complication.

INTRODUCTION

Liver resection (LR) is the gold standard treatment for various liver lesions. Despite its invasive nature, advancements in surgical and anesthetic techniques, minimal access surgery, and perioperative care have improved safety. These developments have expanded the indications for elective LR and significantly reduced postoperative mortality from over 10% to below 5% in recent decades [1-3]. However, postoperative morbidity remains high, ranging from 20% to 45% in different studies [4,5,3].

Procalcitonin (PCT), a 116-amino acid precursor of calcitonin, is normally produced by thyroid C-cells [6]. However, in response to surgery, trauma, or infection, extra-thyroid tissues, including the liver, testis, lungs, and kidneys, express the calcitonin gene (CALC-1), leading to significant PCT production. Hepatic macrophages in the sinusoids are particularly involved in this process [7,8]. After surgery, PCT levels may increase up to 10,000-fold from a baseline of 0.5 Hg/L, independent of steroid administration. It has a half-life of 25-30 hours and reaches peak levels within 18-24 hours post-surgery [9,10,8]. A decrease of more than 30% from the previous day suggests effective treatment and a favorable prognosis, whereas persistently elevated levels indicate a higher risk of complications. PCT also responds faster than CRP in both elevation and clearance [10].

Various criteria have been explored to predict postoperative outcomes following elective LR. These include the "50-50" criterion [11], high bilirubin levels (≥7 mg/dl) [12], and declining serum albumin [13]. Additionally, prediction scores based on the MELD

score and the International Study Group of Liver Surgery definition of post-hepatectomy liver failure (PHLF) have shown low sensitivity and specificity for morbidity and mortality, with limited predictive value before the fifth postoperative day. Moreover, the use of steroids has been shown to suppress common inflammatory markers such as CRP and IL-6, further complicating their use in postoperative prognosis [14].

Serum PCT measurement in the early postoperative period has been identified as a useful prognostic marker after major surgeries, including liver transplantation [15,10,16,17,18]. However, its role in elective LR remains unclear. Studies suggest that measuring PCT within two days of surgery could predict postoperative outcomes [19], with a level of 1.000 µg/L within 12 hours potentially indicating liver failure or complications [20]. Further evaluation is needed to establish its clinical utility. This prospective observational study aimed to assess early postoperative serum PCT levels following elective LR and determine its role in the early detection of complications.

METHODOLOGY

Study Design

This was a single-centered prospective observational study conducted to evaluate patients undergoing elective liver resection at a tertiary hospital.

Study Duration: The study was conducted from July 2021 to June 2024.

Place of Study

The study took place in the Department of Hepatobiliary, Pancreatic & Liver Transplant Surgery at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

Sampling Method

A total of 84 consecutive patients who met the enrolment criteria and underwent elective liver resection were included in the study. Informed written consent was obtained from each patient before surgery for participation.

Data Collection

All relevant patient data were recorded using a structured data collection sheet. Serum samples were collected on the first, third, and seventh post-operative days (POD), and additional samples were taken when necessary.

Laboratory Analysis

Procalcitonin (PCT) levels were measured in the Department of Biochemistry & Molecular Biology, BSMMU, using the Siemens Atellica IM BRAHMS Procalcitonin (PCT) analyzer (reference 11202699) with a measuring interval of 0.03–50.00 µg/L. On the same day, other predictive markers, including white blood cell (WBC) count, C-reactive protein (CRP), and liver and renal function tests, were analyzed.

Grouping of Patients

Patients were divided into two groups based on post-operative complications:

- Group 1: Patients without complications (n = 40)
- Group 2: Patients with complications (n = 44)

Statistical Analysis

Statistical analysis was performed using appropriate software, and results were presented in text and table format according to study objectives.

Ethical Clearance

Formal ethical approval was obtained from the Institutional Review Board (IRB) of BSMMU. The study followed the ethical guidelines of the Declaration of Helsinki, and written informed consent was obtained from all participants before enrolment.

RESULTS

Table 1: Comparison of demographic characteristics of patients between two groups undergoing Elective Liver Resection (N=84)

Characteristics	Group 1 (n= 20)	Group 2 (n= 22)	P value
	n (%)	n (%)	
Age, years, mean ± SD	46.95 ± 13.05	47.05 ± 15.15	[a]o.983[ns]
Sex of the participants			
Male	12 (30%)	30 (68.2%)	[b]0.013[s]
Female	28 (70%)	14 (31.8%)	
BMI, kg/m^2, mean ± SD	21.32±4.09	22.02 ± 3.60	[a]0.806[ns]

P value less than 0.05 is considered statistically significant.

The above table illustrates the comparison of demographic characteristics of all patients between two groups. The mean age of patients in group 1 was 46.95 ± 13.05 years and in group 2 it was 47.05 ± 15.15 years. An independent sample t-test was carried out and the result was statistically not significant (p =0.983).

A Chi-Square test was carried out to find an association between sex and the presence of complications after surgery, and the result was statistically significant (p = 0.013). Male patients experienced more complications than female patients after elective liver resection.

The mean BMI of group 22 patients was 21.32 ± 4.09 kg/m and that of group 2 was 22.02 + 3.60 kg/m". To compare the means, an independent sample t-test was used, and the result was statistically insignificant (p =0.806).

Table 2: Comparison of preoperative performance status of patients between two groups undergoing Elective Liver Resection (N=84)

Characteristics	Group 1 (n= 40)		Group 2 (n= 44)		P value
	n	(%)	n	(%)	
WHO performance status					**0.297^{ns}**
• 0	32	(80%)	30	(63.6%)	
• 1	8	(20%)	10	(22.7%)	
• 2	0	(0%)	6	(13.6%)	
ASA score					**0.123^{ns}**
ASA I	16	(40%)	28	(63.6%)	
ASA II	22	(55%)	10	(22.7%)	
ASA III	2	(5%)	6	(13.6%)	

The above table compares the association of WHO performance status and ASA score between the two groups. A Fisher's exact test was used, and the results were statistically insignificant (p =0.297 and p=0.123, respectively). There was no association between WHO performance status or ASA score and the development of post-operative complications following elective liver resection.

Table 3: Comparison of preoperative hepatic functional status of patients between two groups undergoing Elective Liver Resection (N=84)

Characteristics	Group 1 (n= 40)		Group 2 (n= 44)		P value
	n	(%)	n	(%)	
Child-Turcotte-Pugh score					**1.000**
• A	38	(95%)	40	(90.9%)	
• B	2	(5%)	4	(9.1%)	
MELD score, mean ± SD	6.70 ± 1.30		8.82 ± 3.80		0.021

The above table illustrates any association between the Child-Turcotte-Pugh score and the presence of post-operative complications. Fisher's exact test shows no association between them (p = 1.000).

The mean MELD score of patients in group's 1 and 2 was 6.70 ± 1.30 and 8.82 + 3.80, respectively. An independent sample t-test shows a statistically significant result (p = 0.021). The higher the MELD score, the greater the chance of postoperative complications after liver resection.

Table 4: Comparison of co-morbidities of patients between two groups undergoing Elective Liver Resection (N=84)

Characteristics	Group 1 (n= 40)		Group 2 (n= 44)		P value
	n	(%)	n	(%)	
Co-morbidity	32	(80%)	28	(63.5%)	$^{a}0.241^{ns}$
• Hypertension	16	(40%)	10	(22.7%)	$^{a}0.227^{ns}$
• Diabetes	18	(45%)	6	(13.6%)	$^{a}0.025^{s}$
• Previous upper abdominal surgery	10	(25%)	10	(22.7%)	$^{b}1.000^{ns}$
• Respiratory (Asthma/COPD)	2	(5%)	10	(22.7%)	$^{b}0.187^{ns}$
• Cardiac (IHD)	4	(10%)	4	(9.1%)	$^{b}1.000^{ns}$
• Renal (CKD)	2	(5%)	9	(9.1%)	$^{b}1.000^{ns}$

This table illustrates any association between co-morbidities and postoperative complications after elective liver resection. A Chi-square test shows no association between co-morbidity and complications (p = 0.241). However, diabetes itself was associated with postoperative complications after liver resection (p =0.025). Other co- morbidities had no statistically significant association with post-operative complications.

Table 5: Comparison of pre-operative haematological parameters of patients between two groups undergoing Elective Liver Resection (N=84)

Hematological parameters	Group 1 (n =40)	Group 2 (n=44)	P value
	mean ± SD	mean ± SD	
Hemoglobin, g/dL	11.84 ± 1.31	12.64 ± 2.11	0.144^{ns}
Hematocrit, %	36.67 ± 3.51	38.17 ± 5.63	0.302^{ns}
Red blood cells, $x10^{12}$/L	4.52 ± 0.51	4.52 ± 0.68	1.000^{ns}
WBC, $x10^{9}$/L	8.36 ± 2.03	7.94 ± 2.17	0.521^{ns}
Platelet, $x10^{9}$/L	318.65±89.15	261.32 ± 107.08	0.068^{ns}

The above table shows pre-operative haematological parameters compared between the two groups. An independent sample t-test was carried out each time to compare the means, and each time the results were statistically insignificant (p>0.05). There were no significant differences in haemoglobin, haematocrit, red blood cell count, WBC count, or platelet count between the two groups, which could have contributed to postoperative complications after liver resection. However, a clinically significant reduction in platelet count was seen in group 2 individuals.

Table 6: Comparison of pre-operative biochemical parameters of patients between two groups undergoing Elective Liver Resection (N=84)

Hematological parameters	Group 1 (n =40)	Group 2 (n=44)	P value
	mean ± SD	mean ± SD	
Serum total bilirubin, mg/dL	0.56 ± 0.25	1.57 ± 3.35	0.171^{ns}
Serum albumin, g/L	40.90 ± 4.44	41.21 ± 6.43	0.856^{ns}
PT, seconds	11.54 ± 1.49	12.29 ± 1.96	0.175^{ns}
INR	0.97 ± 0.14	1.02± 0.17	0.279^{ns}
ALT, U /L	31.80±22.71	43.45± 21.60	0.096^{ns}
Serum creatinine, mg/dL	0.86 ± 0.19	1.00± 0.38	0.145^{ns}
eGFR, ml/min/1.73m?	88.55 ± 23.99	92.18± 32.53	0.685^{ns}

The above table shows pre-operative biochemical parameters (liver and renal function tests) compared between the two groups. An independent sample t-test was carried out each time to compare the means, and each time the results were statistically insignificant (p > 0.05). There were no significant differences in serum total bilirubin. Serum albumin, PT, INR, ALT, serum creatinine, or eGFR between the two groups. Which could have contributed to postoperative complications after liver resection.

Table 7: Comparison of different disease characteristics (indications) of patients between two groups undergoing Elective Liver Resection (N=42)

Disease characteristics	Group 1 (n=40)		Group 2 (n=44)		P value
	n	(%)	n	(%)	
Benign	30	(75.0%)	30	(68.2%)	$^{a}0.625^{ns}$
• Hepatolithiasis (Bilateral)	0	(0.0%)	14	(46.7%)	$^{b}0.009^{s}$
• Giant hepatic haemangioma	8	(26.7%)	6	(20.0%)	$^{b}0.691^{ns}$
• Hepatolithiasis (Left)	8	(26.7%)	2	(6.7%)	$^{b}0.174^{ns}$
• Gall bladder mass (e.g., Xanthogranulomatous)	6	(20.0%)	2	(6.7%)	$^{b}0.333^{ns}$
• Hepatic adenoma	2	(6.7%)	2	(6.7%)	$^{b}1.000^{ns}$
• Biliary stricture (post-operative)	2	(6.7%)	2	(6.7%)	$^{b}1.000^{ns}$
• Biliary cystadenoma	2	(6.7%)	0	(0.0%)	$^{b}0.476^{ns}$
• Intrahepatic choledochal cyst	2	(6.7%)	0	(0.0%)	$^{b}0.476^{ns}$
• Simple hepatic cyst	0	(0.0%)	2	(6.7%)	$^{b}1.000^{ns}$
• Malignant	10	(25.0%)	14	(31.8%)	
• Hepatocellular carcinoma	6	(60.0%)	10	(71.4%)	$^{b}0.700^{ns}$
• Gall bladder mass (Malignant)	4	(40.0%)	4	(28.6%)	$^{b}1.000^{ns}$

The above table shows that benign and malignant diseases had no statistically Significant association between the two groups. A Chi-square test was carried out and the p value was 0.625. Among diseases, only hepatolithiasis (bilateral) was significantly associated with postoperative complications after liver resection (p =0.009). All other diseases for which liver resection was performed showed no statistically significant association (p > 0.05).

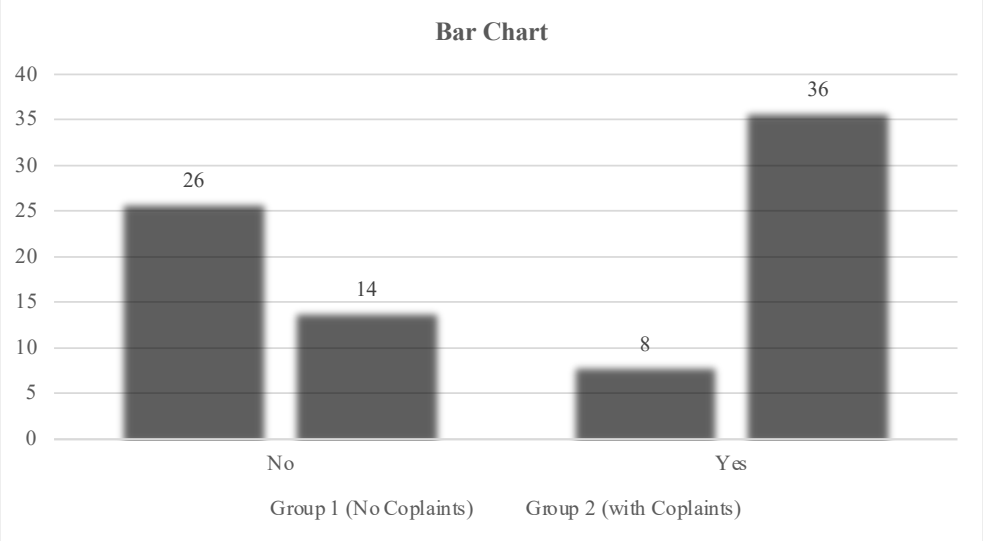

Figure 1: Association between postoperative complications and concomitant intra-abdominal procedures in patients undergoing elective liver resection

The above figure is used to show an association between concomitant Intraabdominal procedures and postoperative complications after elective liver resection.

Table 8: Mean values of all inflammatory markers on POD 1,3 and 7 after elective liver resection in all patients (N=42)

Markers	POD 1	POD 3	POD 7
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
WBC, x 10^9/L	13.55 ± 4.88	9.97± 2.83	8.73 ± 2.83
CRP, mg/L	126.17 ± 50.33	132.34 ± 54.38	68.40 ± 42.37
Serum PCT, ug/L	1.74 ± 2.09	0.62 ± 0.62	0.41 ± 0.51

The above table shows the mean values of all inflammatory markers measured in the mornings of POD 1, 3, and 7 of all patients undergoing elective liver resection. In all patients, the mean WBC count, and the mean serum PCT level declined progressively over time. However, the peak serum CRP level was observed on POD 3 compared to POD 1 and then decreased on POD 7.

Table 9: Comparison of all inflammatory markers on post-operative period in between two groups (N=42)

Markers	Group 1 (n =20)	Group 2 (n=22)	P value
	mean ± SD	**mean ± SD**	
WBC, x 10^9/L			
• POD 1	13.30±3.13	13.77± 6.12	0.755^{ns}
• POD 3	9.85 ±2.68	10.08 ± 3.02	0.799^{ns}
• POD 7	8.01 ±2.51	9.38± 3.0	0.118^{ns}
CRP, mg/L			
• POD 1	130.31 ±50.93	122.40±50.67	0.617^{ns}
• POD 3	125.73 ±50.71	138.34±58.03	0.460^{ns}
• POD 7	66.78 ±39.16	69.88 ±45.96	0.816^{ns}
Serum PCT, ug/L			
• POD 1	0.898 ±0.787	2.508 ±2.587	0.011^{s}
• POD 3	0.314 ±0.249	0.890 ±0.735	0.002^{s}
• POD 7	0.181 ±0.217	0.611 ±0.610	0.005^{s}

The table above Compares the mean values of all inflammatory markers assessed on POD 1,3, a and 7 between the two groups. An independent sample t-test was carried out each time. On POD 1, 3 or 7. The difference in the mean WBC counts between the two groups was not statistically significant (p =0.755, 0.799, and 0.118, respectively). Additionally, there was no statistically significant difference in the mean CRP levels between the two groups on PODs 1, 3, or 7 (p =0.617, 0.460, and 0.816, respectively). However, the mean PCT levels between the two groups were statistically Significant on POD 1, 3, and 7 (p = 0.011, 0.002, and 0.005, respectively).

Table 10: Area Under the Curve (AUC) based on the serum procalcitonin levels measured on post-operative day (POD) 1, 2 and their peak value (N=84)

Test Result Area Variables	Area	Asymptotic 95% CI		Cutoff value, ug/L	Sensitivity, %	Specificity, %	PPV %	NPV %
		Lower Bound	Upper Bound					
POD 1 PCT	0.798	0.660	0.935	1.100	86.4	70.0	74.2	83.7
POD 3 PCT	0.797	0.663	0.930	0.405	72.7	70.0	70.8	71.9
Peak PCT	0.807	0.672	0.942	0.970	86.4	70.0	74.2	83.7

The above table demonstrates the results of the ROC curve (figure 21). The total area under the curve (AUC) for POD 1 serum PCT was 0.798 (95% CI, 0.660, 0.935). The most optimal cutoff of sensitivity and 1-specificity was at a serum PCT level of 1.100 ug/L at which point sensitivity, specificity, PPV, and NPV were 86.4%, 70.0%, 74.2%, and 83.7%, respectively.

The AUC for POD 3 serum PCT was 0.797 (95% CI, 0.663, 0.930). The most optimal cutoff of sensitivity and 1-specificity was at a serum PCT level of 0.405 ug/L at which point sensitivity, specificity, PPV, and NPV were 72.7%, 70.0%, 70.8%, and 71.9%. respectively.

The AUC for peak serum PCT was 0.807 (95% CI, 0.672, 0.942). The most optimal cutoff of sensitivity and 1-specificity was at a serum PCT level of 0.970 ug/L at which point sensitivity, specificity, PPV, and NPV were 86.4%, 70.0%, 74.2%, and 83.7%. respectively.

With the intention of finding an early predictor of complications after elective liver resection, the POD 1 serum PCT level of 1.100 ug/L was selected.

Table 11: Comparison of length of post-operative hospital stay between two groups after Elective Liver Resection (N=84)

Outcome variable	Group 1 (n =40)	Group 2 (n =44)	P value
	mean ± SD	mean ± SD	
Length of hospital stay, days	10.20 ± 4.0	15.86 ± 9.72	0.018[s]

This table shows the length of postoperative hospital stay among all patients who underwent elective liver resection. The mean length of hospital stay was 10.20 ± 4.0 days for group 1 and 15.86 ± 9.72 days for group 2, which was statistically significant (p=0.018) in an independent sample t-test.

DISCUSSION

Liver resection remains a major surgical procedure, with postoperative morbidity rates between 20-45% despite improved safety [21,3]. Early prediction of complications is challenging, as commonly used markers such as the "50-50" criterion, peak bilirubin (≥7 mg/dl), and serum albumin drop have shown limited sensitivity and specificity before POD 5 [13]. Additionally, prediction scores based on the MELD score and the International Study Group of Liver Surgery definition of PHLF have had inconsistent results.

Serum procalcitonin (PCT) is widely recognized as a sepsis marker but has also been identified as a prognostic tool after surgery [10]. Elevated PCT levels have been linked to complications, regardless of age, malignancy, or ASA classification. While some studies recommend measuring PCT within six hours post-surgery for early monitoring [10], our study focused on POD 1 for better predictive accuracy. PCT is commonly used in liver transplant centres for early morbidity prediction [16,18]. Its rise after liver resection results from extra-thyroidal production due to surgical stress, with hepatic macrophages playing a key role [7,8]. This increased PCT production, particularly in patients with pre-existing conditions, can contribute to postoperative inflammation.

Our study demonstrated that PCT is an effective early predictor of complications in Bangladeshi patients undergoing elective liver resection. Among 84 patients, those with a POD 1 PCT level of ≥1.100 µg/L had a significantly higher risk of complications. While peak PCT levels were also analyzed, POD 1 values were more reliable for early detection. Other inflammatory markers like WBC count and CRP were assessed but were not predictive. CRP levels peaked on POD 3, making them unsuitable for early identification of complications.

A recent study set a PCT cutoff of 0.35 µg/L on POD 1 and POD 2 for predicting Clavien-Dindo grade II complications, with 80% sensitivity and 83% specificity [19]. However, this study excluded grade I complications, whereas our study included all complications for comprehensive analysis. Moreover, their cutoff was below the normal baseline of 0.5 µg/L [22], making it impractical. Our cutoff of 1.100 µg/L on POD 1 had a higher sensitivity (86.4%), proving to be a better predictor. Another study measured PCT at 12 hours post-resection in hepatocellular carcinoma patients and set a cutoff of 1.000 µg/L, which correlated with PHLF, sepsis, ICU admission, and mortality [20]. Our study, which included a broader range of liver conditions, found that a similar cutoff (1.100 µg/L) was strongly associated with postoperative outcomes.

However, ICU admissions and mortality were minimal in our cohort.

Most liver resections in our study were performed for benign conditions, particularly hepatolithiasis, which is prevalent in this region. The procedures were safe, with no 30-day mortality, though morbidity was slightly higher (52.4%) than reported in the literature [3,2]. This may be due to thorough postoperative monitoring, ensuring even minor complications were documented.

Complications were significantly associated with male sex, diabetes, bilateral hepatolithiasis, high preoperative MELD scores, and concurrent intra-abdominal procedures such as biliary bypass. Though not statistically significant, a lower platelet count was also observed in patients with complications.

CONCLUSION

Serum PCT T on POD 1 is a strong early predictor of complications after elective liver resections with high sensitivity and moderate specificity. A cutoff value of serum PCT of 1.100 ug/L on POD 1 can accurately predict all kinds of morbidities regardless of the types of diseases.

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