

# Efficacy and Outcomes of Intraoperative Extensive Lavage Plus Surgery Versus Surgery Alone in Patients with Advanced Gastric Cancer: A Multicenter Randomized Controlled Trial

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## Research

**Keywords:** EIPL, advanced gastric cancer, prognosis, recurrence, OS

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# Abstract

**Objective:** This randomized study aims to evaluate the efficacy and long-term outcome of advanced gastric cancer patients with extensive intraoperative peritoneal lavage (EIPL).

**Methods:** A total of 150 patients with advanced gastric cancer were enrolled in this study, the patients were randomly allocated to 2 groups: the group of surgery alone (non-EIPL group), the group of surgery plus EIPL (EIPL group). The surviving rate analysis was compared by the Kaplan–Meier method. The prognostic factors were carried out using the Cox appropriate hazard pattern.

**Results:** Symptom of ileus and abdominal abscess appeared more frequently in the non-EIPL group ( $p < 0.05$ ). The overall survival (OS) curve and the recurrence free survival (RFS) curve of the EIPL group was better than the non-EIPL group ( $p < 0.05$ ). The EIPL, tumor size, vascular invasion, N stage and T stage were independent prognostic factors of overall survival. The independent risk factors of recurrence free survival (RFS) include EIPL and tumor size. Conclusions: The present study revealed that EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. Besides, the overall survival curve and recurrence free survival curve are better in the EIPL group. This technique is easy and not-expensive, therefore EIPL can benefit advanced gastric cancer patients a lot and would be a promising therapeutic strategy in the future.

Trial Registration: Clinical Trials.gov, identifier: NCT02745509, Registered 28 March 2016, <https://clinicaltrials.gov/ct2/show/NCT02745509?cond=NCT02745509&draw=2&rank=1>.

## 1. Introduction

Gastric cancer is one of the most common malignant tumors, its morbidity and mortality in China have been increasing in recent years [1, 2]. Despite great advances in surgery and other treatment, the 5-year survival rate of gastric cancer is low [3, 4]. One of the main problems after resection is its peritoneal dissemination and recurrence, and peritoneal recurrence is more likely to occur in advanced gastric cancer patients. Although chemotherapy is applied, the prognosis of these patients remains poor [5].

There are some free cancer cells that may still exist after resection. In addition, the surgery itself may lead to the dissemination of tumor cells [6, 7], so it is necessary to remove residual tumor cells. Recently, extensive intraoperative peritoneal lavage (EIPL) has got more and more attention, it is a useful treatment which can wash the abdominal cavity completely using 10 L of physiological saline (up to 10 times). Some researchers found that EIPL plus intraperitoneal chemotherapy can improve the prognosis of patients [8], this technique can eradicate peritoneal free cancer which is beneficial for the recurrence free survival (RFS) of gastric cancer patients [9, 10]. However, few studies explored the safety and long outcome of EIPL after curative gastrectomy.

In this research, we explore the efficacy and 3-year outcome of advanced gastric cancer patients with technique of EIPL, and then we analyze the possible mechanism.

## 2. Materials And Methods

### Patients

The study population are advanced gastric cancer patients with clinically T3 or T4, and M0 disease according to computed tomographic scans and ultrasonographic gastroscopy. The seventh American Joint Committee was used for TNM stage. Each patient signed the informed consent, And this study was approved by the institutional review board of the First Affiliated Hospital of Anhui Medical University, Anqing Municipal Hospital and the First Affiliated Hospital of Wenzhou Medical University. All methods were performed in accordance with the relevant guidelines and regulations.

### Inclusion and exclusion criteria

According to the inclusion and exclusion criteria, patients were included in the research. The inclusion criteria included: 1) All patients were confirmed gastric cancer with T3/4NanyM0; 2) the surgery is definite and complete resection of cancer; 3) these patients didn't have heart sickness or any important organ failures; 4) they can keep a long touch with doctors after surgery. The exclusion criteria included: 1) they had previous malignant tumors or various primary tumors; 2) they had accepted radiation treatment or chemo treatment previously before the treatment.

### Procedure

If patients were confirmed cT3 or cT4 and M0 disease and suitable for radical gastrectomy, they will be formally included in the study and then randomized. Patients were randomized in the EIPL group or non-EIPL group in a 1:1 ratio. Allocation was performed using sealed opaque envelopes that contained computer-generated random numbers and the procedure to which patients were allocated. Research participants will be randomized to EIPL arm or non-EIPL arm based on random permuted blocks with varying block size of four, assuming equal allocation between treatment arms. After the exploratory operation, the envelopes were opened to determine whether EIPL was applied. Total gastrectomy or partial resection with D2 lymphadenectomy was performed by the guidelines of the Japanese Research Society [11]. For the non-EIPL group, peritoneal lavage was washed using no more than 3 L of warm saline; In EIPL group, patients received 10 L or more of saline (1 liter at a time) before closure of the abdomen. Patients were excluded if stage were not detected as T3 or T4 and M0, in the end 100 patients were finally included in this study between March 2016 and March 2017. Besides, the external population including 50 gastric cancer patients who were hospitalized in the the First Affiliated Hospital of Wenzhou Medical University and Anqing Municipal Hospital from March 2016 to November 2017, and the methods and procedures are consistent with our group.

### Data collection and follow-up

The data of patients' demographic and clinico-pathological data were recorded, including age, gender, tumor location, tumor size, differentiation grade, pathological type and so on. The pathological tumor

stage was categorized according to the AJCC 7th TNM staging system. The routine laboratory data were listed below: neutrophil, lymphocyte, platelet, CEA and so on.

Peripheral blood tests were obtained within 1 week before surgery and the second days after surgery, the cutoff value of CEA was got according to the normal level. We determine the following indexes (NLR (neutrophil counting/ lymphocyte counting)). These two variables were grouped into low group and high group according to the optimal cut-off values which were calculated based on the Youden index [maximum (sensitivity + specificity-1) [12].

The postoperative complications, the length of hospital stay and other outcomes were also recorded in this research, the complications including abscess, leakage, bleeding and so on.

After the operation, the patients received eight 3-week cycles of oral S-1 plus intravenous oxaliplatin. We got their follow-up date through telephones and outpatient visits. This behavior got carried out in normal intervals (each 90 days within three years), until the date of December 2020.

### **Statistical analysis**

Continuous variables were expressed as mean  $\pm$  standard deviation and they were analyzed by Student T-test; Categorical values were identified by counting (percent) and they were counted by Chi-square test or Fisher exact test. The Kaplan–Meier method was used to compare the prognosis of different groups. The univariate and multivariate analyses were carried out using the Cox proportional hazards model. The whole data explanations got carried out applying SPSS app (17.0 version).

## **3. Results**

### **3.1 Baseline characteristics**

The baseline characteristics analysis of the 150 patients was shown in Table 1, 109 (72.67%) were men, and 41 (27.33%) were women. The median age was 67 years (range, 35–80 years). The basic information in the EIPL group and non-EIPL group had no significant difference. The median follow-up time was 30 months (range 0–45 months). The 1- and 3-year OS rates were 71.0% and 26.5%, respectively.

Table 1  
The baseline characteristics analysis of the patients.

<b>Variable</b>	<b>Non-EIPL group (n = 75)</b>	<b>EIPL group (n = 75)</b>	<b>P</b>
Age(years)	66.93 ± 9.38	64.55 ± 8.22	0.099
Gender			0.200
male	51	58	
female	24	17	
BMI(Kg/m2)	21.51 ± 2.29	21.64 ± 3.34	0.786
smoking			0.373
yes	55	50	
no	20	25	
Tumor location			0.260
upper	21	14	
middle	11	17	
low	43	44	
Differentiated grade			0.121
high	0	0	
middle	55	45	
low	20	30	
T stage			0.405
T3	4	2	
T4	71	73	
N stage			0.112
N0	13	24	
N1	18	12	
N2	14	17	
N3	30	22	
Tumor size(cm)	5.52 ± 2.21	5.37 ± 2.32	0.671
Borrmann classification			0.100

Variable	Non-EIPL group (n = 75)	EIPL group (n = 75)	P
II	7	14	
III	68	61	
CEA(g/L)	16.21 ± 78.06	14.13 ± 35.88	0.834
Neutrophil count(10 <sup>9</sup> /L)	3.49 ± 1.32	4.71 ± 8.39	0.215
Lymphocyte count(10 <sup>9</sup> /L)	1.35 ± 0.47	1.76 ± 2.48	0.164
NLR	3.02 ± 1.96	3.03 ± 2.20	0.989
Platelet(10 <sup>9</sup> /L))	202.52 ± 61.39	226.19 ± 90.94	0.064

## 3.2 Surgical outcome after gastrectomy

Table 2 presented the results of surgery, there were no significant difference in time (surgery to first flatus), postoperative hospital stay, abdominal pain, bleeding, leakage or other blood index between the two groups ( $p > 0.05$ ), but the symptoms of ileus and abdominal abscess appeared more frequently in the non-EIPL group ( $p < 0.05$ ).

Table 2  
The outcome after surgery.

Variable	Non-EIPL group (n = 75)	EIPL group (n = 75)	P
Type of surgery			0.242
total	55	61	
distal	20	14	
Time(surgery to first flatus, days)	4.19 ± 0.99	3.95 ± 0.87	0.108
Postoperative hospital stay(days)	15.26 ± 3.10	14.48 ± 1.97	0.072
Abdominal pain	10/75	5/75	0.174
Ileus	15/75	3/75	0.003
Abdominal abscess	9/75	1/75	0.009
Leakage	5/75	2/75	0.246
Bleeding	6/75	3/75	0.302
Neutrophil count( $10^9/L$ )	10.36 ± 3.32	10.03 ± 3.56	0.552
Lymphocyte cell( $10^9/L$ )	1.02 ± 0.63	1.00 ± 0.60	0.817
NLR	13.48 ± 8.55	11.87 ± 5.22	0.169
Platelet( $10^9/L$ )	171.00 ± 59.98	179.73 ± 60.38	0.381

### 3.3 Overall survival of patients

Risk factors of overall survival are shown in Table 3. The result showed that the EIPL, Borrmann classification, tumor size, N stage, T stage and vascular invasion were significant indicators. Then multivariate analysis revealed that EIPL, tumor size, vascular invasion, N stage and T stage were independent prognostic factors (Table 4). The survival curve (Fig. 1) revealed that the prognosis of EIPL group was better than the non-EIPL group ( $p < 0.001$ ), the 3-year survival rate of EIPL group (38.4%) was higher than the non-EIPL group (21.7%).

Table 3  
Univariate analysis of overall survival.

Variable	$\beta$	HR (95% CI for HR)	P
Gender	0.514	1.671(0.983–2.841)	0.058
Age	0.024	1.025(0.994–1.056)	0.114
EIPL/Non-EIPL	-0.991	0.371(0.218,0.631)	0.000
Tumor size	0.192	1.211(1.088–1.348)	0.000
Type of Surgery	0.185	1.203 (0.653–2.214)	0.553
Tumor location	0.075	0.928(0.689–1.250)	0.622
Borrmann classification	-1.474	0.229(0.072–0.731)	0.013
Differentiated grade	0.491	0.612(0.351–1.067)	0.083
T stage	1.250	3.489(1.094–11.130)	0.035
N stage	0.535	1.707(1.339–2.176)	0.000
Vascular invasion	-0.954	0.385 (0.235–0.632)	0.000

Table 4  
Multivariate analysis of overall survival.

Variable	$\beta$	HR (95% CI for HR)	P
EIPL/Non-EIPL	-0.861	0.423(0.246–0.727)	0.002
Tumor size	0.139	1.149(1.025–1.289)	0.017
Borrmann classification	-0.268	0.765(0.211–2.775)	0.684
T stage	1.395	4.034(1.255–12.971)	0.019
N stage	0.313	1.368(1.034–1.811)	0.029
Vascular invasion	-0.608	0.545 (0.317–0.935)	0.027

### 3.4 Recurrence free survival (RFS) of patients

The risk factor of RFS included EIPL, N stage, vascular invasion, type of surgery, tumor location, borrmann classification and tumor size (Table 5). EIPL and tumor size were independent risk factors (Table 6). The RFS curve of EIPL group was better than non-EIPL group ( $p = 0.004$ ) (Fig. 2), the recurrence rate of EIPL group (24.7%) was lower than the non-EIPL group (46.4%).



Table 5  
Univariate analysis of recurrence free survival.

Variable	$\beta$	HR (95% CI for HR)	P
Gender	0.465	1.592(0.877–2.890)	0.126
Age	0.013	1.013(0.981–1.047)	0.420
EIPL/Non-EIPL	-0.827	0.437(0.245–0.781)	0.005
Tumor size	0.230	1.259(1.212–1.414)	0.000
Type of Surgery	1.081	2.948(1.169–7.438)	0.022
Tumor location	0.422	0.656(0.446–0.964)	0.032
Borrmann classification	1.235	0.291 (0.090–0.936)	0.038
Differentiated grade	0.283	0.753(0.415–1.367)	0.351
T stage	1.028	2.795(0.869–8.993)	0.085
N stage	0.499	1.647(1.257–2.156)	0.000
Vascular invasion	0.768	0.464 (0.265–0.812)	0.007

Table 6  
Multivariate analysis of recurrence free survival.

Variable	$\beta$	HR (95% CI for HR)	P
EIPL/Non-EIPL	-0.769	0.463(0.254–0.846)	0.012
Tumor size	0.171	1.186(1.039–1.354)	0.012
Type of Surgery	0.656	1.927(0.423–8.777)	0.396
Tumor location	0.068	0.934(0.478–1.823)	0.841
Borrmann classification	0.062	0.940(0.236–3.743)	0.930
N stage	0.290	1.337(0.964–1.854)	0.082
Vascular invasion	0.364	0.695 (0.372–1.298)	0.254

### 3.5 Patterns of Recurrence

The recurrence rate of lymph node, node and other organs in the EIPL group and non-EIPL group have no significant difference ( $p > 0.05$ ), but the overall recurrence rate and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group ( $p < 0.05$ ) (Table 7).

Table 7  
The recurrence location after surgery of advanced gastric cancer patients

Variables	Surgery alone (n = 75)	EIPL (n = 75)	P
Peritoneum	17	7	0.026
Lymph node	5	3	0.467
liver	4	2	0.405
lung	3	1	0.311
two place or more	6	4	0.513
total	35	17	0.002

## 4. Discussion

Peritoneal recurrence are associated with prognosis of gastric cancer [13, 14]. Previous researches have reported that EIPL combined with intraperitoneal treatment is effective treatment for gastric cancer patients [15], which can reduce the recurrence rate of advanced patients. However, the safety and effect of EIPL alone remain unclear, so this study explore the clinical value of EIPL.

Our results indicated that the overall survival curve and recurrence free survival curve of EIPL group were better than the non-EIPL group, and technique of EIPL was a significant factor of OS and RFS with advanced gastric cancer patients. So EIPL may reduce the recurrence rate of tumor and improve the outcome of patients. Yamamoto K also conducted an RCT of EIPL with pancreatic cancer patients and got the same conclusion [16]. Based on these researches, technique of EIPL need to be applied in abdominal cancers.

The intraoperative bleeding and surgery itself can lead to the residual tumor cell in the abdominal cavities, and this may increase the risk of peritoneal metastasis. In the non-EIPL group, intraperitoneal lavage does not exceed 3 liters of saline, which may be difficult to remove free peritoneal cancer cells. Technique of EIPL can remove free cancer cells and blood in the abdominal cavity by plenty of washing (10 L or more of saline), which can prevent free cancer cells attaching to the peritoneum [17].

In recent years, there have been several reports [18–20] showing that inflammation was linked to poor survival. Inflammation can stimulate the proliferation of malignant tumors cells, promote metastasis and destroy adaptive immunity response [21]. In this study, we found that the preoperative inflammatory index of NLR in the non-EIPL group was lower than the EIPL group. However, the level of postoperative NLR in the non-EIPL group was higher than the EIPL group. As for the patients with high level of NLR, the anti-tumor immune response of T cells and natural killer cells in the system may be surrounded by a number

of neutrophils, which may decrease the opportunity to contact with tumor cells [22, 23], so the free peritoneal cancer cells may survive in this course.

This study concluded that the symptoms of ileus appeared more in the non EIPL group than the EIPL group. Besides, EIPL can also reduce the possibility of abdominal abscess, but the complications of bleeding and leakage have no significant difference. Indeed, EIPL is similar to the so-called limiting dilution method [24], this technique can clean up the peritoneal effusion and reduce the risk of infection. The 10 times of regular warm saline can promote intestinal motility and functional recovery, and this may also be helpful for surgeons to find the bleeding place. Besides, the level of NLR in the EIPL group was low after surgery, technique of EIPL can reduce the inflammatory cell and cytokines which play an important role in the development of inflammatory response and tissue damage. So technique of EIPL may be beneficial for the perioperative complications and make patients more comfortable after operation.

Although EIPL could not reduce the recurrence rate of lymph node, node and other organs, the overall recurrence rate and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group, besides, the overall survival curve and recurrence free survival curve are better in the EIPL group. Currently, only three RCTs are ongoing to explore the long-term efficacy of EIPL of advance gastric cancer. Kuramoto et al[8] concluded that the peritoneal recurrence rate of the EIPL group was significantly lower than that of the non-EIPL (6.7% vs. 45.8%,  $P = 0.013$ ), there is no difference in recurrence rate for liver transfer, lymph node, and other organ transfer cases between the two groups, which is similar to our study. Another advantage is that IPC is not taken in our study, it may remove side effects associated with chemotherapy and confound the effect of EIPL. Misawa K [25] conducted an RCT indicating that peritoneal recurrence-free survival was not significantly different between the EIPL group and non-EIPL group. The 3-year overall survival rate and RFS rate was better than our study, and the reason is that the proportion of T4 (49.5%) and N3 (28.1%) is smaller than our study population (T4:96.0%, N3:34.7%). The value of EIPL may be related to the stage of T status and N status. The patients of our study (more cases of T4 and N3) have higher risk of recurrence, and the reduction of recurrence rate is significant in the EIPL group. One RCT is still ongoing based in Singapore [26], eligible patients having cT3 or cT4 with M0 disease are also in their criteria, but our study collected more clinical information and explored the safety and efficacy of EIPL group. Our study showed that technique of EIPL can reduce the perioperative complications of patients.

Our study has several limitations. First, we analyze only advanced gastric cancer patients, they may not on behalf of all patients. Second, more cases need to verify our results.

In conclusion, EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. Besides, the overall survival curve and recurrence free survival curve are better in the EIPL group. This technique is easy and not-expensive. Therefore, EIPL can benefit advanced gastric cancer patients a lot and would be a promising therapeutic strategy in the future.

## Abbreviations

EIPL

extensive intraoperative peritoneal lavage

NLR

neutrophils to lymphocytes ratio

PLR

platelets to lymphocytes ratio

OS

overall survival

RFS

recurrence free survival

## Declarations

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None.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Author contributions

Li-xiang Zhang and Chuan-hong Li wrote the main manuscript text, Jun Ma, Lei Chen and Zhi-jian Wei prepared figures and tables. A-Man Xu, Wen-xiu Han conceived and designed the study and assisted in the drafting of the manuscript. All authors have read and approved the final manuscript.

### Corresponding author

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## Ethics approval and consent to participate

this study was approved by the institutional review board of First Affiliated Hospital of Anhui Medical University, Anqing Municipal Hospital and First Affiliated Hospital of Wenzhou Medical University. All methods were performed in accordance with the relevant guidelines and regulations .

Consent for publication Not applicable.

Competing interests

The authors have no conflict of interest to disclose.

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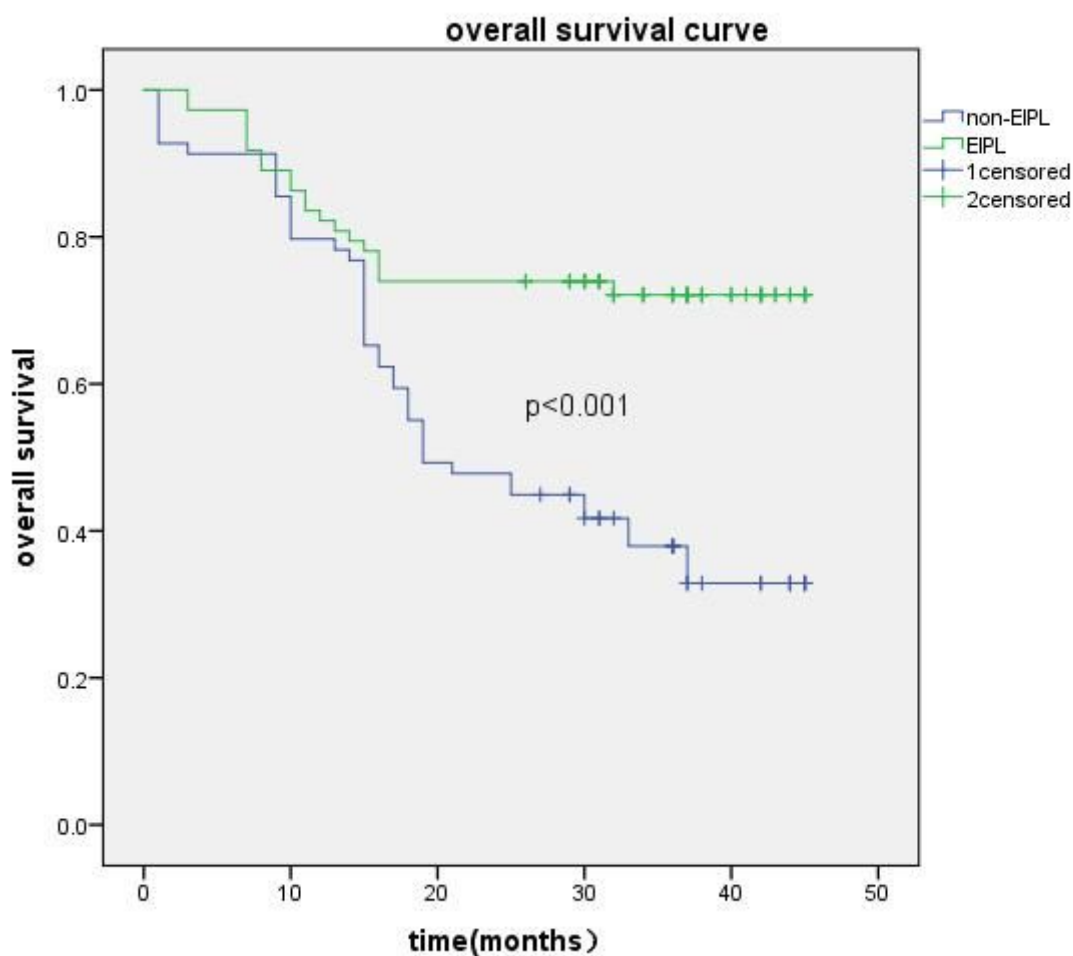
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## Figures



**Figure 1**

The Kaplan–Meier curve of overall survival in the non- EIPL group and EIPL group

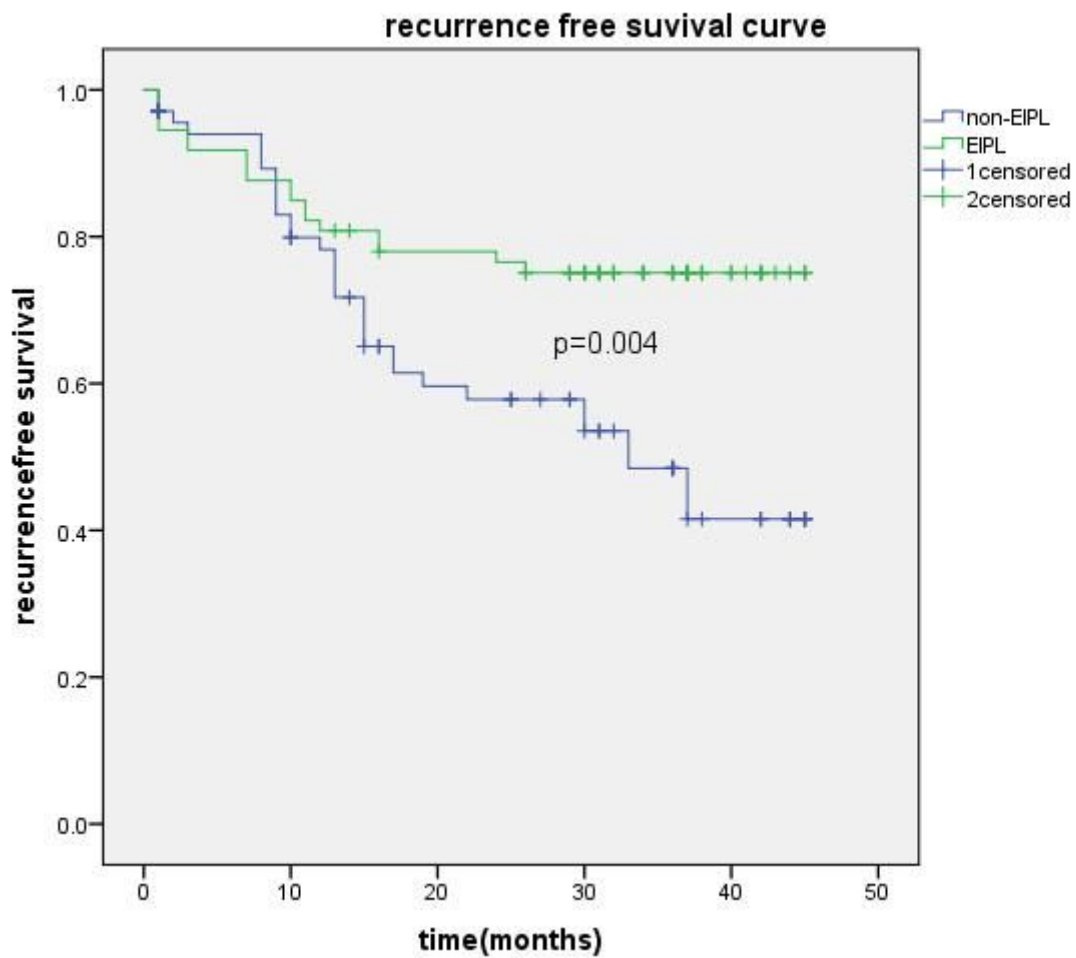


Figure 2

The Kaplan–Meier curve of recurrence free survival in the non-EIPL group and EIPL group