Diplomarbeit

The predictive value of the Neutrophil to lymphocyte ratio, the modified glasgow prognostic score and the CRP to albumin ratio for patients with pancreatic cancer after curative resection. A retrospective single center study

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Eidesstattliche Erklärung

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Graz, am 14.04.17 *Anna Julika Merres eh*

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Abstract

Background: Pancreatic cancer is still considered to be one of the deadliest cancers and curative resection is currently the only curative option. Prognostic factors like the neutrophil to lymphocyte ratio (NLR), the modified Glasgow prognostic score (mGPS) and the CRP to Albumin ratio (CRP/Alb ratio) were already found to be probate indicator tools in various cancer types to categorize patients and foresee their progression. This study investigates the prognostic strength of the factors regarding the overall survival of patients with pancreatic cancer who underwent curative pancreatic resection.

Methods: A total of 202 patients with adenocarcinoma of the pancreas who underwent total resection at the surgical center of the Medical University Graz were subject to a retrospective review. The overall survival was assessed using the method of Kaplan-Meier. Univariate and multivariate Cox regression analysis were applied to predict the prognostic strength of NLR, mGPS and CRP/Alb ratio.

Results: The CRP/Alb ratio is an independent prognostic factor regarding overall survival in univariate and multivariate Cox regression analysis. It is associated with a higher Charlson Index, a higher UICC classification, an increased CEA level and preoperative symptoms (especially preoperative pancreatitis, jaundice and weight loss). NLR and mGPS were associated with a decreased overall survival only in univariate analysis. Additional factors associated with a worse outcome were lymph node involvement, metastasis and a higher UICC classification.

Conclusion: The CRP/Alb ratio is a useful prognostic factor for the prediction of overall survival for patients who suffer from pancreatic cancer after pancreatic resection. It also proves to be superior to the other prognostic factors investigated, NLR and mGPS. Based on the potential benefit, individual risk assessment based on the CRP/Alb ratio should be considered in the future.

Zusammenfassung

Hintergrund: Das Pankreaskarzinom ist bis heute eine der tödlichsten Krebserkrankungen und derzeit stellt Resektion des Pankreas die einzige kurative Therapieoption dar. Prognostische Faktoren, wie der Neutrophils to lymphocytes ratio (NLR), der modified Glasgow prognostic score (mGPS) und der CRP to Albumin ratio (CRP/Alb ratio) wurden in der Literatur bereits als probates Mittel zur Kategorisierung von Patienten/Patientinnen bezogen auf ihr Gesamtüberleben beschrieben. Die vorliegende Studie untersucht die drei Faktoren hinsichtlich ihrer prognostischen Stärke auf das Überleben von Patienten/Patientinnen mit Pankreaskarzinom nach Pankreasresektion.

Methoden: Die Retrospektive Studie umschloss 202 Patienten/Patientinnen mit Pankreaskarzinom, die mittels kurativer Pankreasresektion in der Allgemeinchirurgischen Abteilung der medizinischen Universität Graz therapiert wurden. Die prognostische Stärke der Faktoren NLR, mGPS und CRP/Alb ratio wurde mittels univariater und multivariater Cox Regressionsanalyse bezogen auf das Überleben der Patienten ermittelt.

Ergebnisse: Die CRP/Alb ratio zeigte sich als unabhängiger prognostischer Faktor für das Überleben des Patientenkollektivs sowohl in multivariater, als auch in univariater Analyse. Außerdem war er assoziiert mit einem höheren Charlson Index, einer höheren UICC Klassifikation, einem erhöhten CEA Level und präoperativen Symptomen (insbesondere präoperative Pankreatitis, Iketrus und Gewichtsverlust). NLR und mGPS zeigten sich nur in univariater Analyse als signifikanter prognostischer Faktor. Weitere Faktoren, die mit geringerem Gesamtüberleben assoziiert sind waren betroffene Lymphknoten, Metastasierung und eine höhere UICC Klassifikation.

Schlussfolgerung: Die CRP/Alb ratio ist ein sinnvoller prognostischer Faktor für das Gesamtüberleben von Patienten/Patientinnen mit Pankreaskarzinom nach Pankreasresektion. Außerdem scheint sie anderen prognostischen Faktoren, wie dem

NLR und dem mGPS überlegen. Somit könnte die CRP/Alb ratio in Zukunft zum Einschätzen des individuellen Risikos im klinischen Alltag eingesetzt werden.

List of abbreviations

AJCC	American Joint Committee on cancer
ASA	American Society of Anaesthesiology
CAR	C-reactive protein/Albumin ratio
CA 19-9	Carbohydrate antigen 19-9
CCI	Charlson Comorbidity Score
CEA	Carcinoembryonic antigen
CRP	C-reactive protein
CT	Computer tomography
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
G	Grading
M	Distant metastasis
mGPS	Modified Glasgow prognostic score
MRCP	Magnet resonance cholangiopancreatography
N	Regional lymph nodes
NLR	Neutrophils to lymphocyte ratio
PDAC	Ductal adenocarcinoma of the pancreas
PET	Positron emission tomography
PNI	Perineural invasion
PSCs	Pancreatic stellate cells
R	Resection
T	Primary Tumour

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1. Introduction

1.1 Pancreatic cancer in Austria

In Austria, pancreatic cancer accounts for 1583 newly diagnosed cases per year. Although ranking in at the fourth common cause of all cancer-related deaths (8%) in both male and female, it is very low on the list of cancer sites in terms of incidence (4% of all carcinoma). In the past couple of years, treatment strategies have dramatically started to show impact: 1 and 2 year survival rates have significantly increased, yet still the 5 year survival rate does not succeed 10%. [1] Therefore, of all the gastrointestinal cancer, Pancreatic cancer has the worst prognosis.

The symptoms of pancreatic cancer are rather unspecific und vary from case to case. Nevertheless, the main symptoms are jaundice (50%), weight loss (60%) and abdominal pain (80%). Abdominal pain is a sign of a locally advanced tumour since it results from tumour infiltration of the neural plexus surrounding the proximal superior mesenteric artery and celiac axis terminating in the celiac ganglia. [2]

Both environmental and hereditary factors contribute to the development of pancreatic cancer, whereas smoking seems to be the most significant risk factor. Approximately 25% of all cases of pancreatic cancer are associated with heavy cigarette smoking.[3] Furthermore obesity, diabetes mellitus, a history of pancreatitis, heavy alcohol consumption (<60 mL ethanol/day) and a family history of pancreatic cancer are associated with a high risk of pancreatic cancer. [4]

1.2 Ductal Adenocarcinoma of the Pancreas

Approximately 90% of all cases are found to be ductal adenocarcinoma of the pancreas (PDAC), a rapidly progressive and late diagnosed exocrine cancer. [5] PDACs arise from precursor lesions, that can either be microscopic (pancreatic intraductal neoplasia) or macroscopic cystic precursor lesions (intraductal papillary mucinous neoplasm, mucinous cystic neoplasm). PDACs characteristically present as ill-defined,

white-yellow, solid masses and are histologically characterized by infiltrating glandular and ductal structures. Enlarged nuclei with hyperchromasia and the production of mucin, similar to the ductal cells they originated from, are typical features of these carcinoma cells. [5] [2] The neoplastic cells form glands, infiltrate into tissue and form tongues of neoplastic cells that reach well beyond the main tumour into neighbourly structures. Thus, almost all PDACs invade nerves, spread along perineural spaces. Additionally, invasion of regional lymph nodes lead to early metastasis into the liver. [6]

Enclosing the PDAC one can typically find desmoplastic Stroma building a structural framework. The neoplastic PDAC cells interact with the surrounding stromal cells to create a unique microenvironment supporting tumour progression [7]. Proinflammatory signals stimulate the recruitment of inflammatory cells and the proliferation of pancreatic stellate cells (PSCs). Upon stimulation PSCs transform into a matrix producing myofibroblasts and therefore contribute to the excess fibrosis formation surrounding the tumour. [8] In vivo and in vitro studies have shown that PSCs promote immune evasion, chemoresistance and the recurrence of the pancreatic carcinoma. [9]

1.3 Diagnosis of the ductal adenocarcinoma of the pancreas

Since most patients with PDAC do not show any early symptoms, every pain in the upper abdominal region is a situation worthy of clarification. The predominant cause for jaundice (20%) in patients above the age of 60 is pancreatic cancer and therefore any case of newly diagnosed jaundice should also be screened for PDAC. [10] Other signs could be the development of diabetes or malabsorption, although not all newly diagnosed cases of diabetes and/or malabsorption should automatically lead to screening for pancreatic cancer. Also, substantial obstruction of the pancreatic duct can lead to acute pancreatitis. Therefore, acute pancreatitis without known risk factor has to be assessed with detailed radiological imaging. [11]

Ultrasound of the abdomen should be the first choice for detection followed by a CT abdomen to identify pancreatic neoplasms. Once a pancreatic mass has been identified

and seems to be resectable, resection should be performed as quickly as possible by a hepatobiliary surgeon.

A high CA19-9 tumour marker value, routinely used in the diagnosis of pancreatic carcinoma, can sometimes be associated with a larger tumour mass and a laparoscopic staging can be indicated. Tissue samples can be bioptically obtained to histologically categorize the neoplasm if necessary. Staging examinations besides ultrasound of the abdomen include multidetector CT, endoscopic ultrasound, thoracic CT, Positron emission tomography (PET) scan, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) and MR cholangiopancreatography (MRCP).

1.4 Stages of pancreatic cancer

The staging system for pancreatic cancer is based on the American Joint Committee on cancer (AJCC) TNM system. It is based on three key pieces of information; T describes the size of the main tumour and its location, N describes the spread to nearby lymph nodes and M shows whether the tumour has metastasized. In table 1 the different TNM categories are summarized.

Table 1: TNM categories, modified from The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system for pancreatic cancer [12]

T categories
TX: The main tumour cannot be assessed. **T0:** No evidence of a primary tumour. **Tis:** Carcinoma in situ (the tumour is confined to the top layers of pancreatic duct cells). **T1:** The cancer has not grown outside the pancreas and is 2 cm or less across. **T2:** The cancer has not grown outside the pancreas but is larger than 2cm across **T3:** The cancer has grown outside the pancreas into nearby surrounding structures but not into major blood vessels or nerves. **T4:** The cancer has grown beyond the pancreas into nearby large blood vessels or nerves.
N categories
NX: Nearby (regional) lymph nodes cannot be assessed. **N0:** The cancer has not spread to nearby lymph nodes. **N1:** The cancer has spread to nearby lymph nodes.
M categories
M0: The cancer has not spread to distant lymph nodes (other than those near the pancreas) or to distant organs such as the liver, lungs, brain, etc. **M1:** The cancer has spread to distant lymph nodes or to distant organs.

Table 2:UICC categories, modified from The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system for pancreatic cancer [12]

Stage	Stage grouping	Stage description
0	Tis, N0, M0	The tumour is confined to the top layers of pancreatic duct cells and has not invaded deeper tissues. It has not spread outside of the pancreas. These tumours are sometimes referred to as pancreatic carcinoma in situ or pancreatic intraepithelial neoplasia III (PanIn III).
IA	T1, N0, M0	The tumour is confined to the pancreas and is 2 cm across or smaller (T1). The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).
IB	T2, N0, M0	The tumour is confined to the pancreas and is larger than 2 cm across (T2). The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).
IIA	T3, N0, M0	The tumour is growing outside the pancreas but not into major blood vessels or nerves (T3). The cancer has not spread to nearby lymph nodes (N0) or distant sites (M0).
IIB	T1-T3, N1, M0	The tumour is either confined to the pancreas or growing outside the pancreas but not into major blood vessels or nerves (T1-T3). The cancer has spread to nearby lymph nodes (N1) but not to distant sites (M0).
III	T4, Any N, M0	The tumour is growing outside the pancreas and into nearby major blood vessels or nerves (T4). The cancer may or may not have spread to nearby lymph nodes (Any N). It has not spread to distant sites(M0).
IV	Any T, Any N, M1	The cancer has spread to distant sites (M1).

1.5 Therapy of the ductal adenocarcinoma of the pancreas

Total resection of the tumour is the only therapy for PDAC with curative intent, whereas only 15 - 20% of all patients are applicable to resection. [13] The 5-year survival after total resection is about 18 - 27%, nevertheless patients with R0 resections are

associated with a significantly better prognosis. [14-18] It is important to state that locally advanced tumours should be resected en-bloc with the adjacent organs, since the advanced R0 resection has the same prognosis as the standard resection. [19-22] Excluded from resection are patients with distant metastatic disease which make out 53% of all patients. [23] The possibilities of resection depend on progression and the location of the tumour. Under no circumstances is any intrusion of the pancreatic cancer in the coeliac axis, the superior mesenteric artery or a patent superior mesenteric-portal venous confluence allowed to be evident in order to have any chance of resection. [11]

Depending on which study is considered, 65 - 78% of all PDAC are located in the head, 15-18% in tail and body of the pancreas, while the rest are diffuse, originating from the gland or unspecified. [24]

Regarding PDAC of the head, a partial pancreaticoduodenectomy with or without preserving of the pylorus or in rare cases a total pancreatectomy is performed. For carcinoma in the tail a distal pancreatectomy and for tumours of the body a distal pancreatectomy or a pancreaticoduodenectomy are common.

At most expert centres, operative mortality is low. Postoperative complications only occur in approximately 40% of all cases and include pancreatic anastomotic leaks, haemorrhage, development of intraabdominal abscess, delayed gastric emptying or wound infection. [25]

1.6 Common prognostic factors

Identifying different prognostic factors has been the topic of a lot of studies and the following factors have been found to play an important role in terms of recurrence-free and long-term survival.

Tumour size can be determined preoperatively and are part of the current TNM staging system discriminating T1 and T2 tumours. In general, it was found that survival is decreasing with increased tumour size. However small tumours (<2cm) may still be associated with a poor outcome depending on the individual tumour biology. [26] Larger

tumours are also linked to margin positivity following pancreatic surgery and therefore to local tumour recurrence. [27]

Tumour grade and lymph node involvement are also powerful prognostic factors. Patients without affected lymph nodes show a superior median survival than patients with lymph node positivity. There is also a clear survival difference between local or distant lymph node metastases, whereas para-aortic lymph node involvement is an independent factor for a poor prognosis. The ratio of metastatic to examined lymph nodes (LNR) of >0,3 has a negative impact on long-term survival. [26] Wasif et al. showed that high tumour grade has a larger effect on the prognosis than both tumour size and lymph node involvement reflecting the important role of the tumour biology. They should therefore be included in the TNM staging. [28]

Invasion of major retroperitoneal blood vessels occurs regularly due to the anatomic location of the pancreas and is an independent predictor of poor survival. Resection of affected venous branches of the mesenterico-portal axis is no clear surrogate for irresectability, while arterial resection seldomly yields a favourable outcome and therefore should only be considered in very particular cases. [29]

Perineural invasion (PNI) is closely related with a worse longterm survival after surgical resection and might also predict early cancer recurrence. The severity of the PNI was also found to correlate strongly with the rate of survival. [30]

Unlike expected, age alone does not seem to be a negative prognostic factor. In fact, advanced age is not a risk factor for negative outcome in curative pancreatic cancer surgery and therefore elderly patients should not be excluded from curative surgery. The biological age of each individuum reflected by different established clinical scoring systems such as ASA classification, Charlson Comorbidity Index etc. seems to be more suitable to predict the risk of pancreatic resection than numeric age alone in a geriatric surgical population. [31]

CA 19-9 (Carbohydrate antigen 19-9) and CEA (Carcinoembryonic antigen) are tumour markers used routinely in the diagnosis of pancreatic carcinoma. Neither marker has the accuracy for screening asymptomatic populations but can be used when there is a

possibility of PDAC in addition to the clinical examination and imaging techniques. [32] In addition CA 19-9 has been used as a prognostic marker. CA 19-9 levels have been shown to predict survival in patients suffering from PDAC, whereas a CA 19-9 value of > 37 U/L is linked to a decreased survival. [33] There also appears to be a correlation between lower levels and resectable PDAC and higher levels is a biomarker higher levels of CA 19-9 and unresectable conditions. [34] An increase in the postoperative CA 19-9 serum level is a biomarker for tumour recurrence after curative pancreatic resection for PDAC; a decrease of CA 19-9 levels after resection predicts a better outcome. [35]

CEA levels of <5 ng/ml have been found to be associated with benign pancreas formations, whereas levels of >5 ng/ml seems to correlate with pancreas malignancies but since sensitivity is only 45%, CEA should only be used for patients with suspicious clinical features. [36] Nevertheless a mathematical combination of both CA 19-9 and CEA can significantly improve the prognostic prediction in patients with PDAC. [37]

1.7 Novel Prognostic factors

Inflammatory processes play an important role in the development of tumours and the systemic inflammatory response is recognised as an important factor in many types of malignancies including pancreatic cancer. [38] Malignancies themselves are also known to trigger an inflammatory response resulting in deleterious effects such as cachexia. [39] The novel prognostic factors discussed below are therefore based on elements of the inflammatory response.

Leucocytes, including lymphocytes as well as neutrophils, were demonstrated to be involved in tumour inflammation and immunology. [40] [41] Neutrophils were shown to produce proangiogenic factors that lead to tumour progression. Interleukin-6 and tumour necrosis factor alpha are present in the tumour environment and may promote neutrophilia.

The presence of infiltrating Neutrophils in the tumour was shown to be correlated with poor outcome, whereas lymphocyte infiltration is associated with a better prognosis. [42] [43] Therefore, an elevated neutrophil to lymphocyte ratio may be a potential risk factor for poor outcome of patients suffering from PDAC. The correlation between the NLR and poor outcome has already been reported for patients suffering from colon cancer, lung cancer, renal cell carcinoma, liver cancer and PDAC.[44-47] It also seems that the NLR is significantly higher in advanced stages of cancer, as well as advanced UICC stages, pT stages, lymph node invasion and poor tumour differentiation. [48]

The optimal cut-off value for NLR is yet to be discussed, since numerous studies showed very different cut off values. An et al. as well as Garcea et al. and Stotz et al. showed that the best cut-off value was NLR > 5, whereas an optimal cut-off value of NLR > 2 was described by various other studies [45, 48-50]. NLR>3 and NLR > 4 were also considered to be a poor prognostic factor for survival [51] [52].

Another factor that can be calculated is the modified Glasgow prognostic score (mGPS). It is a score which combines an elevated C-reactive protein (CRP) level with hypoalbuminemia while a score of 1 equals an elevated CRP level (>10 mg/l) and a score of 2 is given for an elevated CRP and hypoalbuminemia (<35 g/l). An isolated hypoalbuminemia has no prognostic value and is therefore not included in the score. [53] It has been shown that an elevated mGPS is an independent predictor for survival for patients undergoing potentially curative pancreatic resection. [54] [55]

The CRP to albumin ratio (CAR) constitutes a third prognostic parameter that this study focuses on. It has been shown, that the CAR is a reliable factor for the outcome of patients with all different kinds of cancer including pancreatic cancer. [56-59] The cut off value is yet to be determined. Wu. et al showed the optimal cut-off value at 0.54, whereas Haruki et al. proposed an optimal cut-off value of 0.03. [60, 61]

1.8 Aim of this study

The purpose of this study was to evaluate patients with PDAC after curative resection regarding different prognostic factors in terms of survival and post-operative complications. We focused on easily calculated not yet firmly established factors such as the NLR, mGPS and CAR and to evaluate if they could be introduced in clinical routine as predictive factors for the outcome of patients suffering from PDAC who were scheduled for surgical resection.

2. Methods

This retrospective study was conducted as a single-center-analysis at the department of general surgery of the medical university Graz.

All data from patients with resectable ductal pancreatic adenocarcinoma that underwent pancreatic surgery between january 2000 and december 2016 at the department of general surgery Graz, were included. Patients with other tumour entities or unresectable PDACs were excluded from the study. Patients with missing data relevant for this study were also excluded (Figure 1). For deceased patients data were collected from the Austrian national cancer registry. [62]

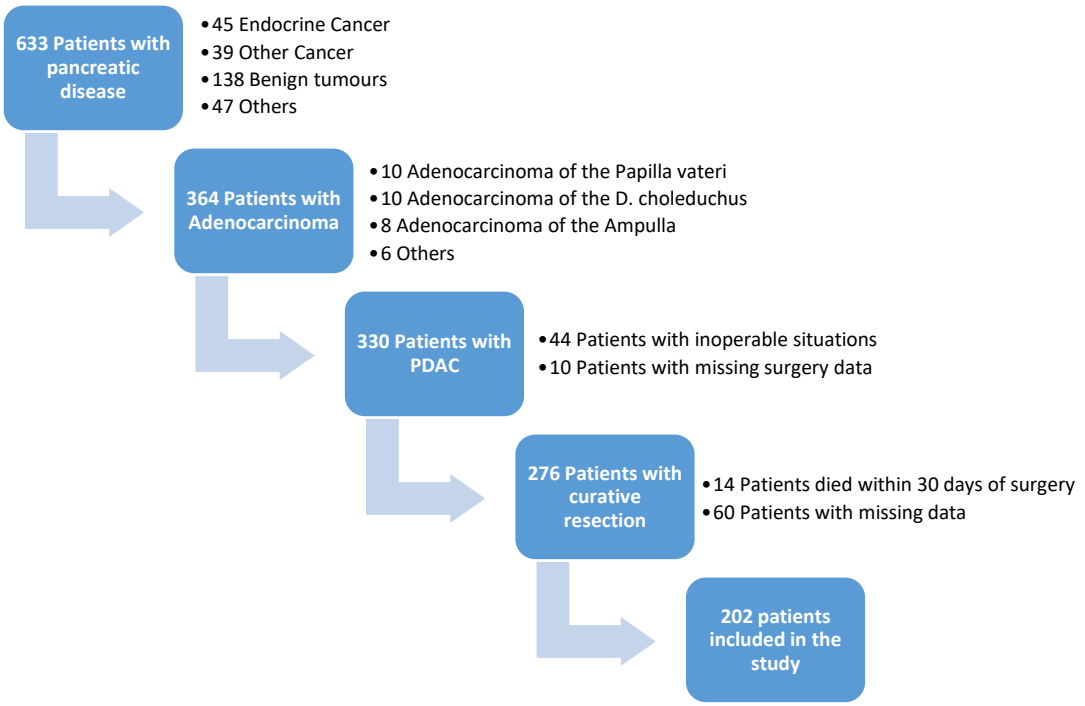


Figure 1: Patient collective

The study protocol was approved by the local ethics committee (25-303 ex 12/13).

2.1 Data Collection

Patient data were retrospectively collected from the digital hospital database “Medocs”. The data were anonymized and summarized in an excel work sheet. The following clinical and pathological parameters were obtained:

1. Demographic patient’s data (Date of birth, age, sex, weight, height)

2. Preoperative symptoms, risk factors and comorbidities (jaundice, abdominal pain, emesis, weight loss, pancreatitis, diabetes, nicotine abuse, alcohol abuse, cardiovascular-, pulmonary-, gastrointestinal comorbidities, other malignancies)
3. Preoperative laboratory results (Leucocytes, neutrophils, monocytes, thrombocytes, lymphocytes, CRP, total protein, albumin, total bilirubin, CA 19-9, CEA, Lipase, Amylase)
4. Radiological methods (CT, MRT, PET-CT, MRCP, ERCP)
5. Surgery data (Type of surgery performed, date of surgery, surgery time, intraoperative complications)
6. Pathological data (TNM classification, UICC classification, histological grading, perineural invasion, lymphatic invasion, size of tumour, tumour location)
7. Follow up time, overall survival time

2.2 Patient categorization

The patient collective was categorized by different factors, including ASA category and the Charlson comorbidity index. These factors were assigned as follows.

The ASA physical status classification was preoperatively established as shown in table 3.

Table 3: ASA physical status classification system[63]

ASA 1	A normal healthy person
ASA 2	A patient with mild systemic disease
ASA 3	A patient with severe systemic disease
ASA 4	A patient with severe systemic disease that is a constant threat to life
ASA 5	A moribund person who is not expected to survive without an operation
ASA 6	A declared brain-dead person whose organs are being removed for donor purposes

The charlson comorbidity index (CCI) is a prognostic index that classifies or weighs comorbid conditions. It has been validated for various diseases including cancer for its ability to predict mortality. It consists of 17 comorbidities, that are weighted from 1 to 6 and then summed up to combine the CCI:

One point:	Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes
two points:	Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumour, leukaemia, lymphoma
three points:	Moderate or severe liver disease
six points:	Malignant tumour with metastasis, AIDS

Since the CCI was conducted retrospectively the following criteria were applied. One point for Diabetes mellitus, cardiovascular-, gastrointestinal- and pulmonary comorbidities. Three points were applied for hypalbuminaemia (< 3.5 g/dl) combined with an increased bilirubin concentration (> 1.1 mg/dl) as a sign for chronic liver disease. Two points were used for haematological malignancies and six points for extrapancreatic malignancies, as well as metastatic disease.

2.3 Calculation of the prognostic factor

The NLR was calculated by division of the absolute numbers of neutrophils and lymphocytes. The CRP to albumin ratio was likewise calculated by division of the CRP and the albumin value. The optimal cut-off values of either the NLR and the CRP/Alb ratio regarding follow up time were defined and the patients categorized into groups.

The mGPS combines elevated CRP- and decreased albumin values. Patients with an increased CRP (>10 mg/dl) and a decreased albumin value (<3.5 g/dl) were given a mGPS score of 2, patients with only an increased CRP a score of 1 and patients with neither a score of 0 (Table 4). [64]

Table 4: Inflammation based prognostic score mGPS

	mGPS 0	mGPS 1	mGPS 2
CRP	< 10 mg/dl	> 10 mg/dl	> 10 mg/dl
Albumin	≤ 3.5 g/dl	≤ 3.5 g/dl	< 3.5 g/dl

2.4 Statistics

The statistics were generated with SPSS 23.0 for windows (IBM Inc. Somers, USA). Follow up time and overall survival time were calculated from the date of surgery to the date of the last known examination in a hospital being part of the KAGES group or verified death respectively.

First, the complete roster of patients was categorized into two or three groups according to the cut-off values of the different prognostic parameters NLR, mGPS and CRP/Alb ratio. Long-time overall survival was calculated according to the methods of Kaplan and Meier curve; a log-Rank test was performed to establish significant differences between subgroups.

The relationship between the prognostic factors, the overall survival time and clinico-pathological parameters was determined using univariate and multivariate analysis. For categorical data, chi square test was conducted, for numeric data t-test or Mann-Whitney U test (depending on the distribution of the data) was performed. Univariate and multivariate analysis was performed using COX regression analysis to assess the influence of the different clinico-pathological parameters on the follow up time. A two-sided $p < 0.05$ was considered statistically significant.

3. Results

Only patients which fit the criteria of resectable ductal adenocarcinoma of the pancreas were considered in this study. Patients who had died within thirty days after tumour resection as well as patients with missing data were excluded from the focus of all further studies. Patient selection is shown in figure 1.

3.1 Patient data

3.1.1 Demographic Data

A total of 202 patients were included in the study. The median age was 65.1 years (with a range from 41 to 84) with 73 patients older than 70. Among the patients almost half (101 patients, 52.9%) were male and half (90 patients, 47.1%) were female. The median BMI was 25.2 kg/m^2, ranging from 14.8 – 40.7 kg/m^2. Patients were also divided by their ASA score. Most patients had an ASA score of 3 (50.8 %) followed by 2 (38.2%), 4 (6.8%) and 1 (4.2%).

Table 5:Demographic Data

Age [a]	Median: 65.1 [41 – 84]
> 70 a	73 (36.1%)
Male	103 (51%)
Female	99 (49%)
BMI [kg/m^2]	Median: 25.0 [14.8 – 40.7]
ASA	
1	8 (4%)
2	79 (39.1%)
3	97 (48%)
4	14 (6.9%)

3.1.2 Preoperative symptoms and risk factors

In Table 6 preoperative symptoms, as well as risk factors and comorbidities were summarized. All in all, 129 (63.9%) patients suffered from preoperative symptoms. Patients exhibited abdominal pain (43.6%) and jaundice (35.1%) were most often described at initial presentation, followed by weight loss (24.3%), preoperative pancreatitis (10.9%), diarrhoea (8.4%) and emesis (76.9%). 23.3% suffered from diabetes, 12.9% from chronic pancreatitis, 20.8% stated to be smokers and 17.4% admitted to drinking alcohol on a regular basis.

Table 6: Preoperative symptoms and risk factors

Preoperative Symptoms		Yes 129 (63.9 %)
	Abdominal Pain	88 (43.6%)
	Jaundice	71 (35.1%)
	Weight loss	49 (24.3%)
	Preoperative pancreatitis	22 (10.9%)
	Diarrhoea	17 (8.4%)
	Emesis	14 (6.9 %)
Risk factors		n (%)
	Alcohol abuse	35 (17.4%)
	Nicotine abuse	42 (20.8%)
	Chronic pancreatitis	26 (12.9%)
	Diabetes	47 (23.3%)
Comorbidities		n (%)
	Cardiovascular comorbidities	123 (60.9%)
	Other comorbidities	70 (34.7%)
	Gastrointestinal comorbidities	43 (21.3%)
	Extra-pancreatic malignancies	34 (17.8%)
	Pulmonary comorbidities	31 (15.3%)
Charlson Comorbidity Index		Median: 4.4 [0 – 19]

The most common comorbidities were cardiovascular comorbidities (60.9%), gastrointestinal comorbidities (21.3%), extra-pancreatic malignancies (17.8%) and

pulmonary comorbidities (15.3%). All comorbidities can be combined into the Charlson Index. The medium Charlson Index for the described patient collective was 4.4 ranging from 0 to 19.

3.1.3 Patient collective categorization by tumour location and the type of surgery performed.

Most PDAC were located in the caput of the pancreas (67.9%), 12.9% were located in the corpus, 6.4% in the cauda and 1 % in the papilla. 9.9% hat various or diffuse locations. The following surgeries were performed. 74 (39.7%) Pylorus-preserving pancreatoduodenectomy, 53 (26.2%) classical whipple operations, 33 (16.2%) total pancreatectomies and 41 (20.3%) distal pancreatectomies.

Table 7: Location of the tumour and the type of surgery performed

Location of the tumour	n (%)
Caput	117 (57.9%)
Corpus	26 (12.9%)
Cauda	13 (6.4%)
Papilla	2 (1%)
Diffuse	12 (9.9%)
Type of surgery	n (%)
Pylorus-preserving pancreatoduodenectomy	74 (36.7%)
Classical Whipple	53 (26.2%)
Total Pancreatectomy	33 (16.3%)
Distal Pancreatectomy	41 (20.3%)
Central Pancreatectomy	1 (0.5%)

3.1.4 TNM and UICC Classification

All tumours can be categorised by the TNM classification. Most patients showed a T of 3 (88.1%), meaning that the cancer has grown outside the pancreas into nearby surrounding structures but not into major blood vessels or nerves. The main body of patients showed regional lymph node metastasis (77.7%) and 17.3% had distant metastasis. (Table 8)

Table 8: TNM classification of the patient collective

Primary tumour T		**Grading G**	
n (%)		**n (%)**	
T 1	8 (4%)	G 1	9 (4.5%)
T 2	6 (3%)	G 2	100 (49.5%)
T 3	178 (88.1%)	G 3	89 (44.1%)
T 4	9 (4.5%)	G 4	2 (1%)
Regional lymph nodes N		**Distant metastasis M**	
n (%)		**n (%)**	
N 0	45 (22.3%)	M 0	167 (82.7%)
N 1	157 (77.7%)	M 1	35 (17.3%)

Table 9 shows the patient collective divided by their UICC classification. Most patients showed an UICC classification IIA (12.9%) or IIB (62.4%).

Table 9: UICC classification of the patient collective

UICC	**n (%)**
IA	5 (2.5%)
IB	2 (1%)
IIA	26 (12.9%)
IIB	126 (62.4%)
III	9 (4.5%)
IV	33 (16.3%)

3.1.5 Follow up times, overall survival and days spent in hospital care

The median follow up time for this patient collective was 23.4 months, ranging from 1 to 148 months. The median overall survival time was 19.3 months and the average hospital stay was 23.4 days, ranging from 2 to 77 days (Table 10)

Table 10: Follow up times, overall survival and days spent in hospital care

Follow up time [m]	Median: 23.4 [1 – 148]
Overall survival time [m]	Median: 19.3 [1 – 79]
Hospital stay [d]	Median: 26.8 [2 – 77]

3.2 The neutrophil to lymphocyte ratio

3.2.1 Cumulative survival using Kaplan-Meier curve regarding NLR

Figure 2 shows the cumulative survival for the different cut off values of NLR regarding overall survival time. There is no statistical difference for NLR>3, NLR>4 or NLR>5, whereas patients with a NLR>2 (n=153) had (p=0,068) lower overall survival times than patients with a NLR<2 (n=49).

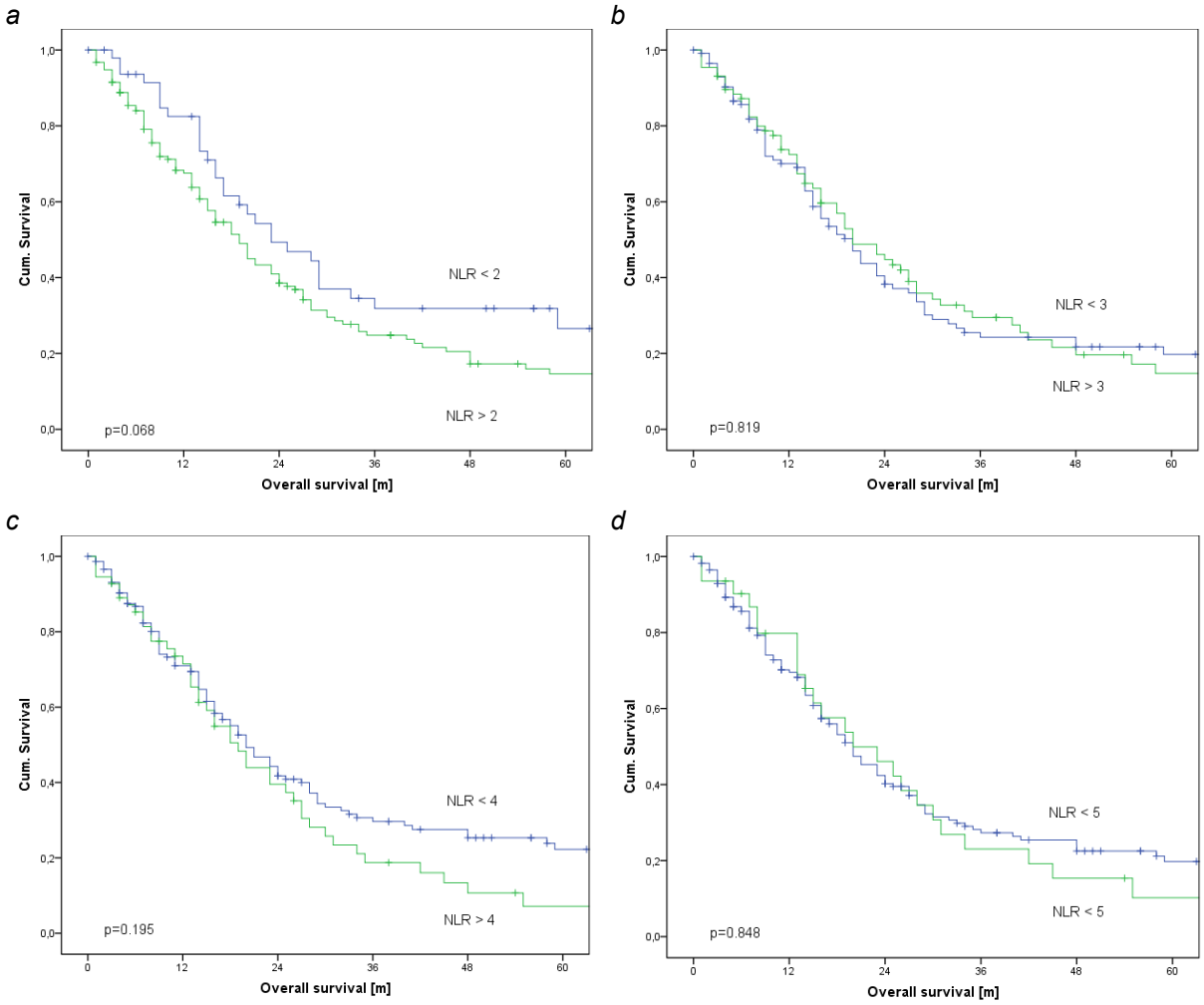
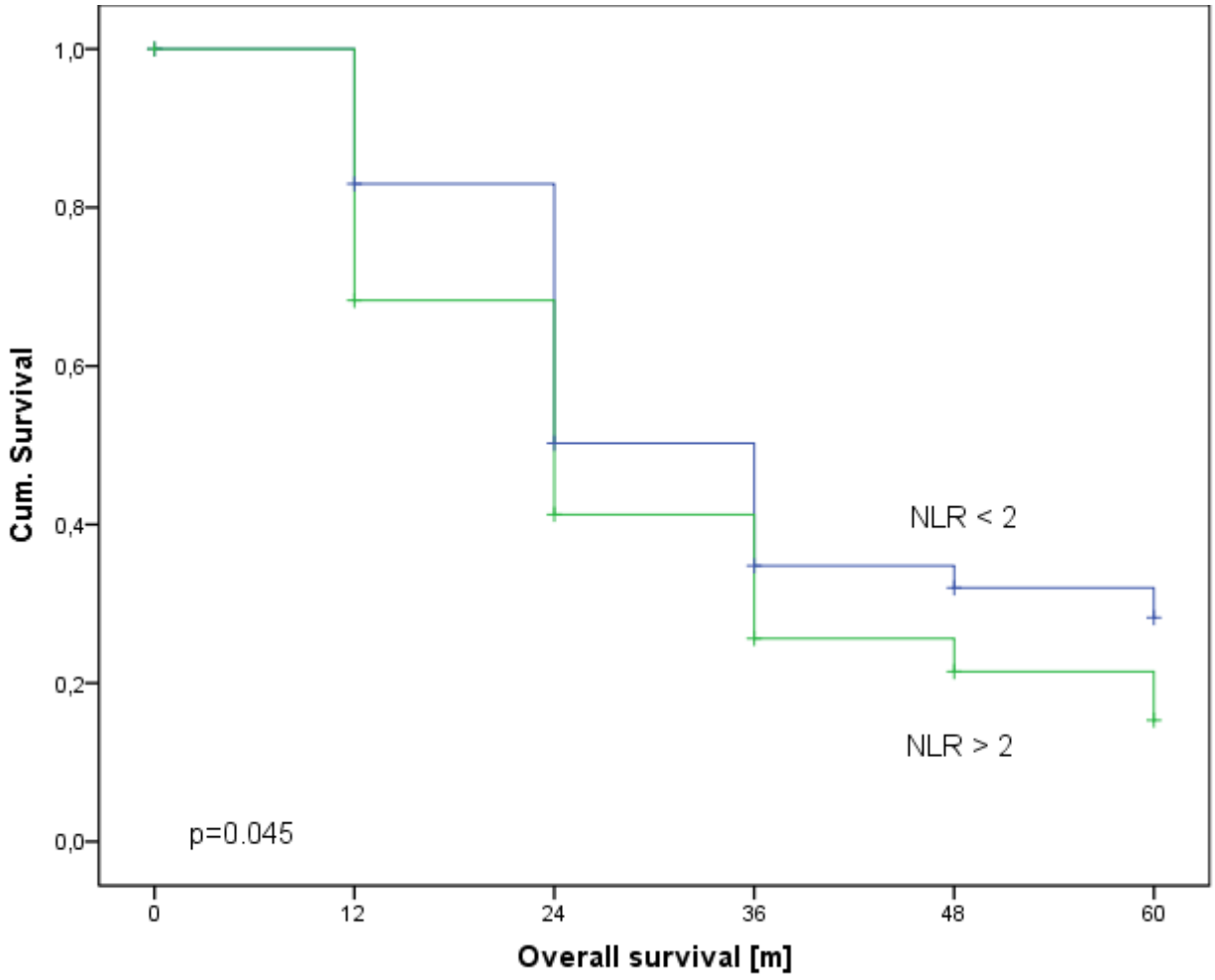


*Figure 2: Cumulative survival for the different cut off values for NLR regarding follow up time a) NLR>2 p=0.068, b) NLR>3 p=0.819, c) NLR>4 p=0.195, d) NLR>5 p=0.848 (p<0.05 *, P<0.01 **, p<0.001 ***)*

For the remainder of the study only a cut off value of 2 was considered.

In Figure 3 the mortality table for patients with NLR < 2 (blue) and patients with NLR > 2 (green). Patients with a lower NLR have significantly lower mortality rates (p = 0.045) than patients with a higher NLR. The 1 year and 5 year survival rate is higher for patients with a NLR < 2.



Patients at risk					
NLR < 2	35.5	19.5	12.5	8.5	3
NLR > 2	88	47.5	24.5	17.5	7.5

	1 year survival	5 year survival
NLR < 2	75%	10%
NLR > 2	59%	7%

Figure 3: Mortality table of patients with NLR < 2 vs. Patients with NLR > 2. The Patients at risk and 1 year/5 year survival are stated below. Patients with NLR < 2 have a higher 1 year and 5 year survival rate than patients with a NLR > 2.

3.2.2 Univariate analysis of clinico-pathological parameters in correlation to NLR

As shown in table 11, for a NLR with a cut-off of 2 the follow up time is reduced for patients with a NLR ≥ 2. For patients with a NLR < 2 the median overall survival time is 20.8 months, whereas for patients with a NLR ≥ 2 it is 2 month less (18.8 months). For the parameters hospital stay, age, CA 19-9 and CEA there was no significant difference.

*Table 11: Univariate analysis of clinico-pathological parameters for patients with NLR ≥ 2 and Patients with NLR< 2 (p<0,05 *, P<0,01 **, p<0,001 ***)*

	NLR < 2 mean	**NLR ≥ 2 mean**	**p**	**Significance**
Age [y]	64.4	65.3	0.572	-
Overall Survival [m]	20.8	18.8	0.511	-
Follow up [m]	28.4	21.7	0.074	-
Hospital stay [d]	27.8	26.1	0.427	-
CA19-9 [U/ml]	457.5	2222.1	0.206	-
CEA [ng/ml]	3.4	6.2	0.123	-

Univariate analysis with chi square test (table 12) showed that there was no statistical difference between patients with NLR<2 and NLR>2 regarding Sex, ASA criteria, CA 19-9 and CEA level, as well as T-, R-, M- or N category and a higher grading. It was shown, that a Charlson comorbidity Index > 2 and preoperative symptoms, especially jaundice and preoperative pancreatitis are significantly correlated with patients with a NLR > 2 in comparison to patients with NLR< 2

*Table 12: Univariate analysis (chi square test) of clinico-pathological parameters for patients with NLR ≥ 2 and Patients with NLR< 2 (p<0.05 *, P<0.01 **, p<0.001 ***) 1: CEA and CA 19-9 values were only available from 149 patients.*

	NLR < 2 n [%]	**NLR > 2 n [%]**	**p**	**Sig.**
Age >70	16 [8%]	57 [28%]	0.560	-
Female	27 [13%]	72 [36%]	0.327	-
Charlson Index >2	21 [10%]	91 [45%]	0.042	*
Morbidity	12 [6%]	36 [18%]	0.796	-
ASA > 2	31 [15%]	80 [40%]	0.179	-
CA19-9 > 37 kIU/L[1]	23 [15%]	83 [56%]	0.418	-
CEA > 3,8 µg/L[1]	9 [6%]	38 [27%]	0.458	-
R category 1	21 [10%]	54 [32%]	0.144	-
N category 1	35 [17%]	122 [60%]	0.224	-
Grading 3/4	26 [13%]	65 [32%]	0.195	-
T 3/4	45 [22%]	142 [70%]	0.821	-
M category 1	7 [3%]	28 [14%]	0.507	-
UICC IIB/III/IV	37 [18%]	131 [65%]	0.100	-
Preoperative symptoms	21 [11%]	108 [56%]	0.001	***
Jaundice	7 [4%]	64 [33%]	0.001	***
Weight loss	14 [7%]	35 [18%]	0.372	-
Preop. Pancreatitis	1 [1%]	21 [11%]	0.029	*

3.3 The Modified Glasgow Prognostic Score

3.3.1 Cumulative survival using Kaplan-Meier curve regarding mGPS

The patient collective was divided into two groups, regarding their mGPS (0,1 or 2) and follow up times were compared using Kaplan-Meier method (Figure 4: Cumulative survival of patients divided by mGPS=0 (blue), mGPS= 1 (green) and mGPS=2 (red). Patients with a mGPS of 2 (n=17) had a significantly poorer outcome regarding follow up time than patients with a mGPS of 0 (n= 94) or 1 (n=32). There was no difference between patients with a score of 0 and patients with a score of 1.

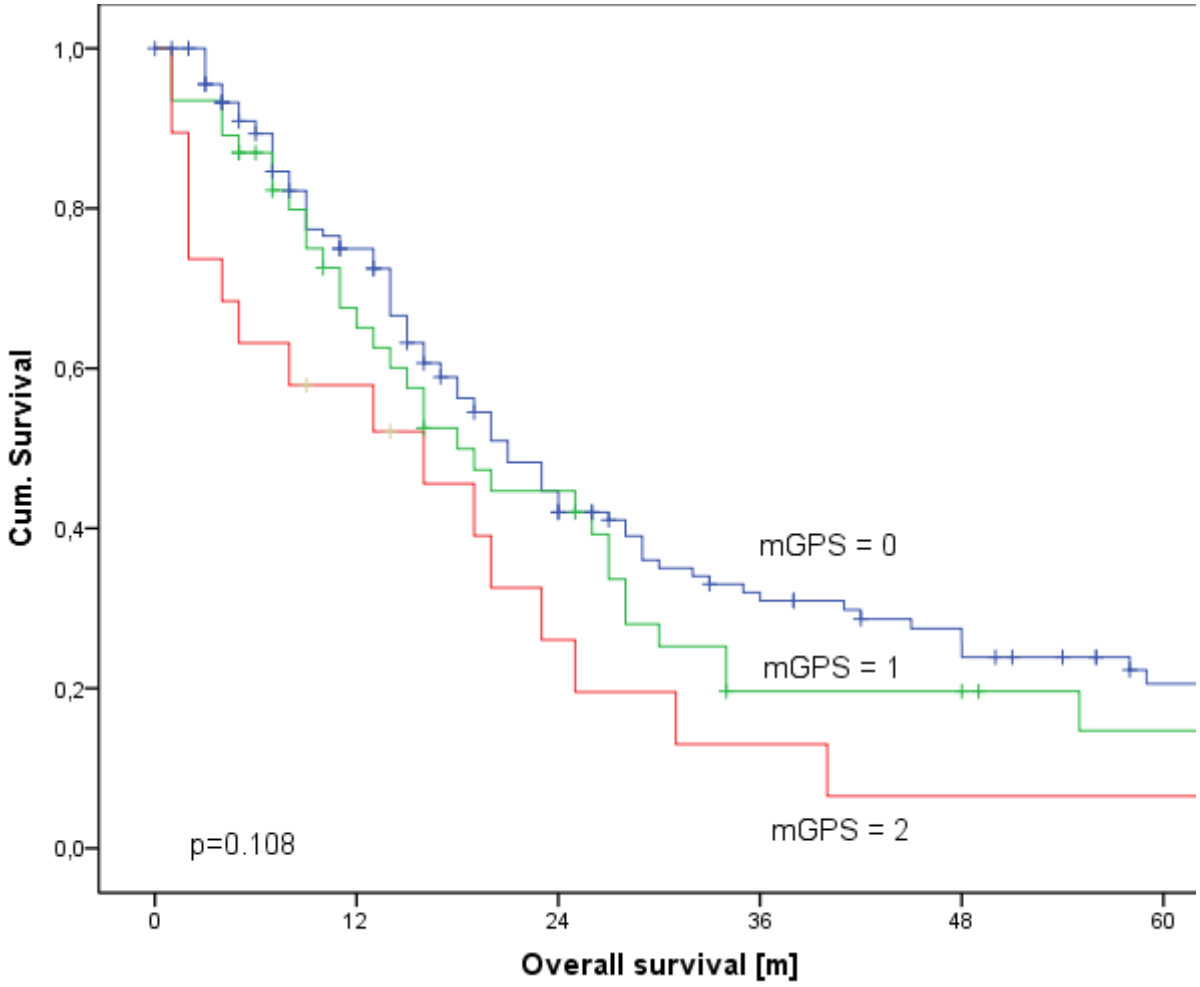


Figure 4: Cumulative survival of patients divided by mGPS=0 (blue), mGPS= 1 (green) and mGPS=2 (red). There was no significant difference between the groups regarding overall survival time.

Figure 5 shows the cumulative survival of both patients with a mGPS of 0 or 1 (blue) compared to patients with a mGPS of 2 (green). Patients with a mGPS of 2 have significantly shorter survival times than patients with mGPS = 0 or 1.

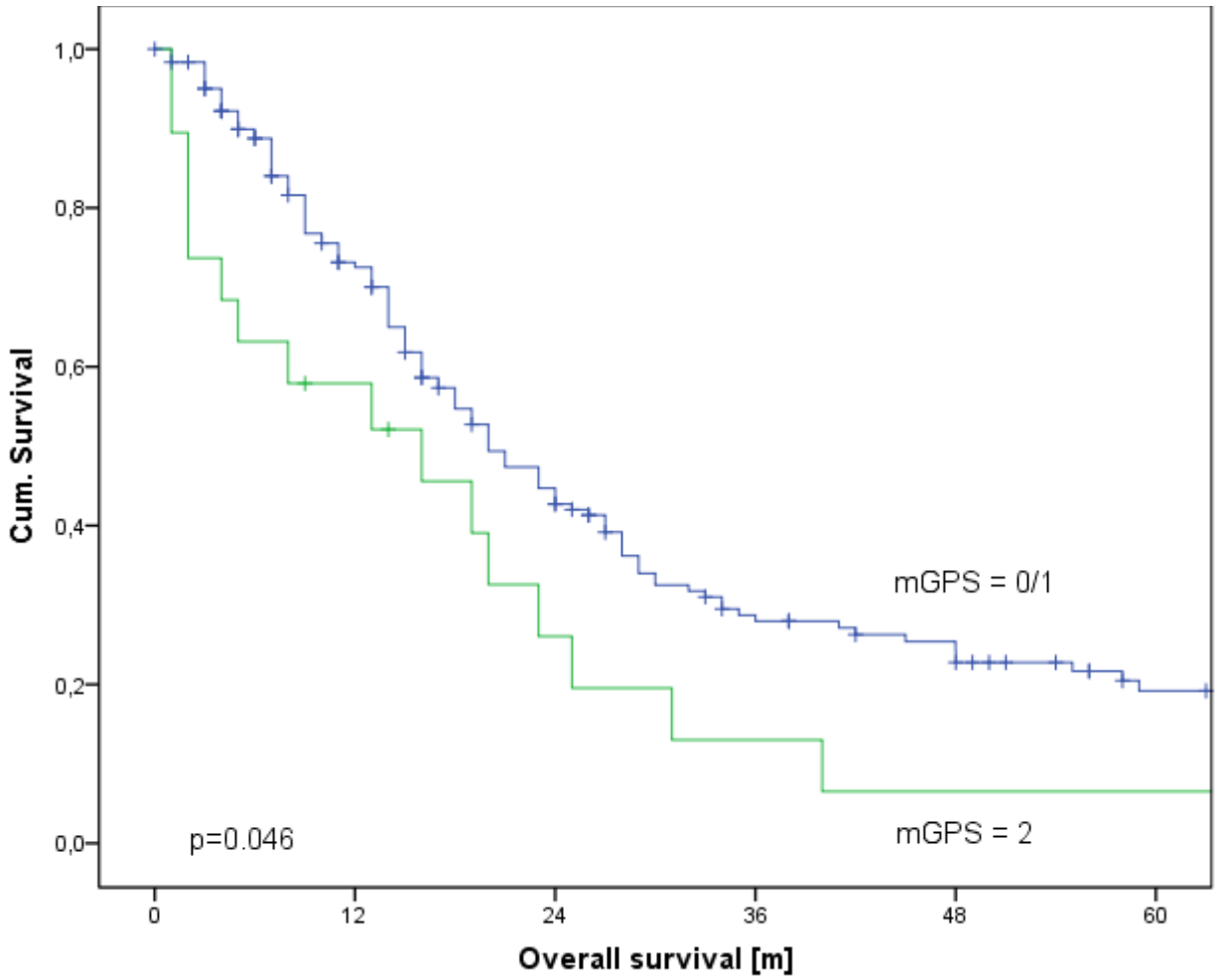
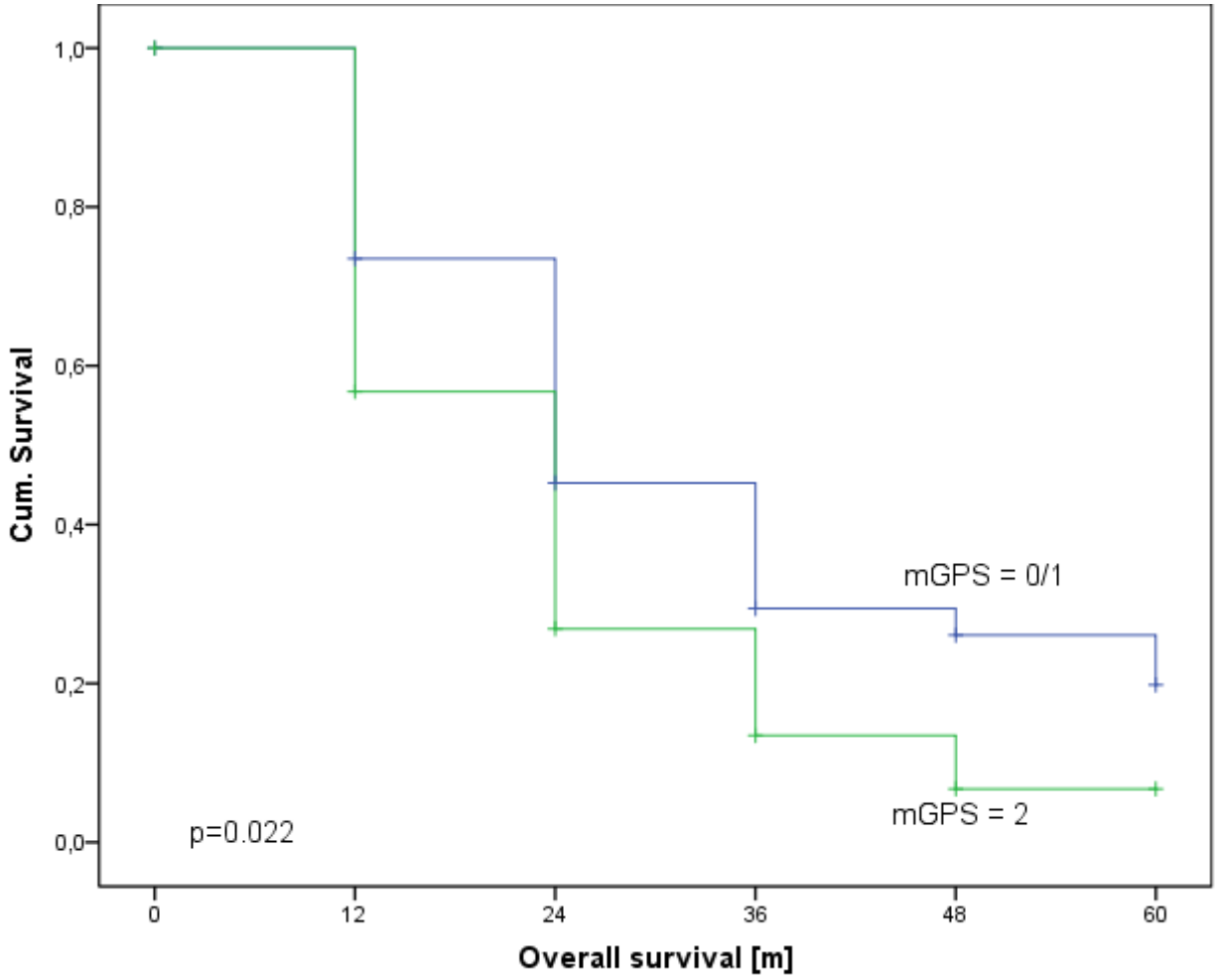


Figure 5: Cumulative survival for patients with mGPS 0 and 1 combined vs. patients with mGPS = 2. Patients with a mGPS of 2 have a significantly shorter survival time than patients with a mGPS of 0 or 1.

The mortality table (figure 6) shows a significant difference between patients with a mGPS of 0/1 compared to patients with a mGPS of 2. The one-year survival of patients with a mGPS = 0/1 was 64% whereas patients with a mGPS = 2 had a one-year survival of 53%. The five-year survival of patients with mGPS = 2 was 0.5%, patients with a mGPS = 0/1 had an 8% chance of survivng five years.



Patients at risk					
mGPS = 0/1	114.5	63	35	25	10
mGPS = 2	9.5	4	2	1	0.5

	1 year survival	5 year survival
mGPS = 0/1	64%	8%
mGPS = 2	53%	0.5%

Figure 6: Mortality table of patients with mGPS = 0/1 vs. Patients with mGPS 2. The Patients at risk and 1 year/5 year survival are stated below. Patients with mGPS = 0/1 have a higher 1 year and 5 year survival rate than patients with a mGPS = 2.

3.3.2 Univariate Analysis of clinico-pathological parameters in correlation to mGPS

Table 13 shows, that with increasing mGPS the days spent in hospital rise significantly. The mGPS is also significantly correlated with CEA. The mGPS is not correlated with Age, overall survival or follow up time or CA 19-9.

*Table 13: Univariate analysis of clinico-pathological parameters for patients with mGPS=0, mGPS=1 and mGPS=2 (p<0.05 *, P<0.01 **, p<0.001 ***)*

	mGPS=0 mean	mGPS=1 mean	mGPS=2 mean	p	Significance
Age	65.7	62.8	66.6	0.127	-
Survival [m]	21.2	16.6	13.1	0.122	-
Follow up [m]	24.8	21.9	16.7	0.164	-
Hospital stay [d]	25.4	27.1	33.3	0.048	*
CA19-9 [kUI/L]	2326.8	741.3	764.5	0.251	-
CEA [µg/L]	4.79	5.63	12.2	0.045	*

Table 14: shows that a Charlson Index >2 and an occurrence of preoperative symptoms (especially jaundice) are significant pathological parameters correlated with the mGPS. There is no significant difference between the different groups and female patients, patients with an age > 70 year, the occurrence of morbidity after surgery, an ASA > 2, an elevated CEA or CA 19-9 value, a R, N or M Category of 1 or a higher grading (3 and 4) with reference to mGPS.

*Table 14: Univariate analysis (chi square test) of clinico-pathological parameters for patients with mGPS=0, mGPS=1 and mGPS=2 (p<0.05 *, P<0.01 **, p<0.001 ***)*

	mGPS=0 n [%]	mGPS=1 n [%]	mGPS=2 n [%]	p	Sig.
Age >70	55 [27%]	11 [5%]	7 [3%]	0.140	-
Female	64 [32%]	24 [12%]	11 [5%]	0.585	-
Charlson Index >2	71 [35%]	23 [11%]	18 [9%]	0.001	**
Morbidity	30 [15%]	12 [6%]	6 [3%]	0.549	-

ASA > 2	75 [37%]	25 [12%]	11 [5%]	0.963	-
CA19-9 > 37 kIU/L	70 [47%]	23 [15%]	13 [9%]	0.151	-
CEA > 3.8 µg/L	27 [19%]	14 [10%]	6 [4%]	0.097	-
R category 1	51 [30%]	17 [9%]	7 [4%]	0.945	-
N category 1	101 [50%]	39 [19%]	17 [8%]	0.128	-
Grading 3/4	65 [32%]	19 [9%]	7 [4%]	0.578	-
T 3/4	125 [62%]	44 [22%]	18 [9%]	0.572	-
M category 1	24 [12%]	8 [4%]	3 [1%]	0.980	-
UICC IIB/III/IV	109 [54%]	41 [20%]	18 [9%]	0.119	-
Preoperative symptoms	79 [41%]	33 [17%]	17 [9%]	0.007	**
Jaundice	37 [19%]	19 [10%]	15 [7%]	0.0001	***
Preop. pancreatitis	11 [6%]	7 [4%]	4 [1%]	0.132	-

3.4 The CRP to Albumin ratio

3.4.1 Cumulative survival using Kaplan-Meier curve regarding CRP/Alb ratio and CRP, Albumin alone

The optimal cut-off value for the CRP to Albumin ratio for this patient collective is 0.0003 and was determined using ROC curve analysis. Figure 7 shows the Kaplan-Meier curve for Patients with a CAR<0.0003 (blue, 143 patients) vs. patients with a CAR > 0.0003 (green, 59 patients).

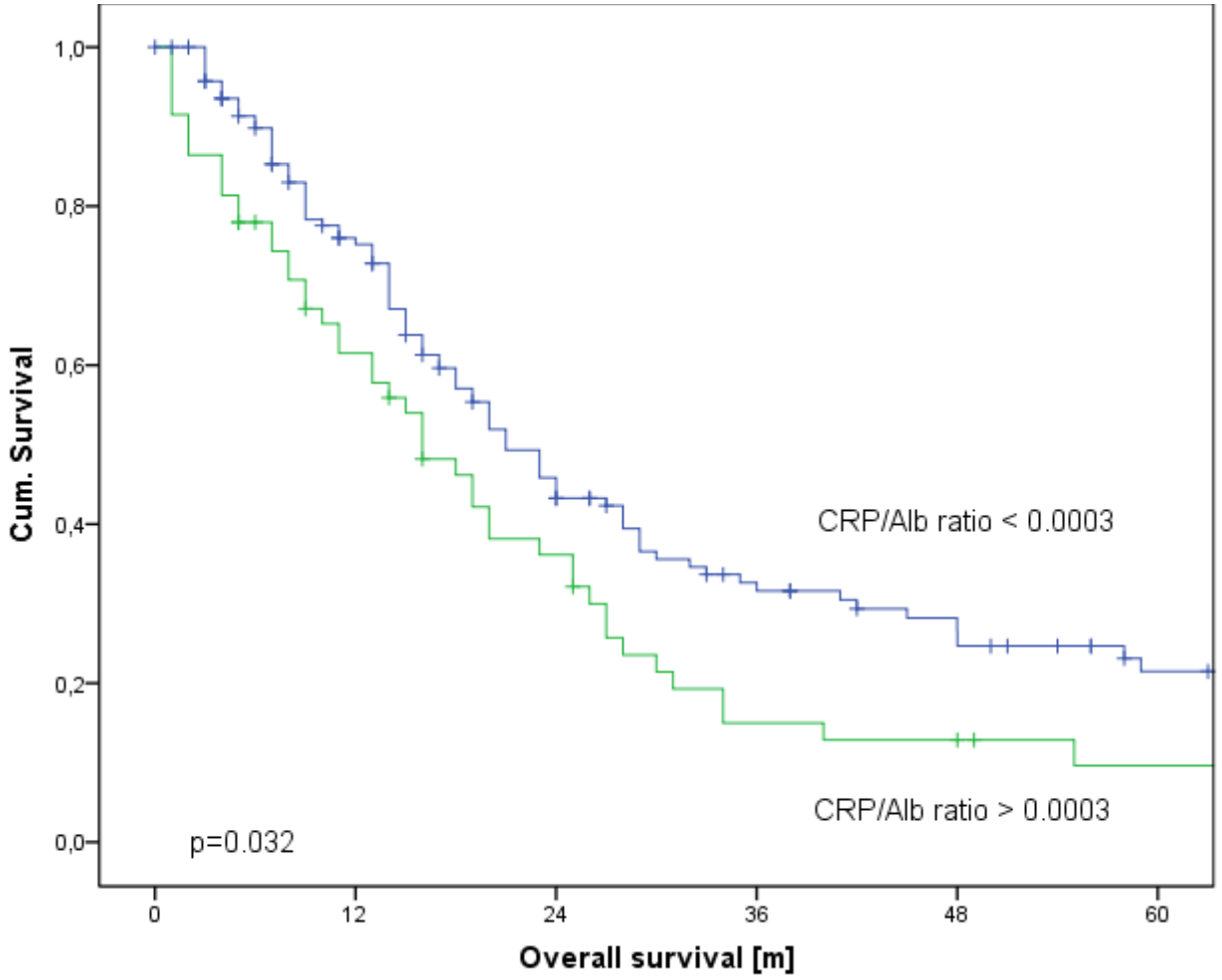


Figure 7: Cumulative survival for patients with a CRP/Albumin ratio > 0.0003 (green) vs. patients with a CRP/Alb ratio < 0.0003 (blue). Patients with a higher CRP/Alb ratio showed a significantly shorter overall survival time (p=0.032).

In Figure 8 the Kaplan-meier curves for elevated serum CRP and hypalbuminaemia are shown. The cut-off value for CRP of 9.77 mg/l was obtained using ROC analysis. In comparison to the CRP/alb ratio the two factors alone do not show a significant consequence on the patient's overall survival time.

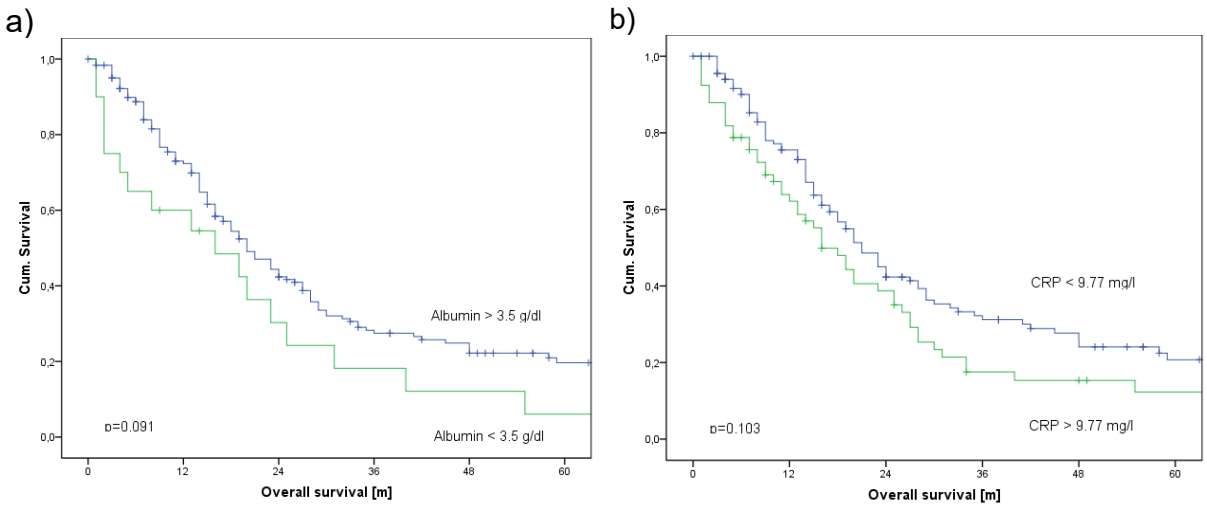
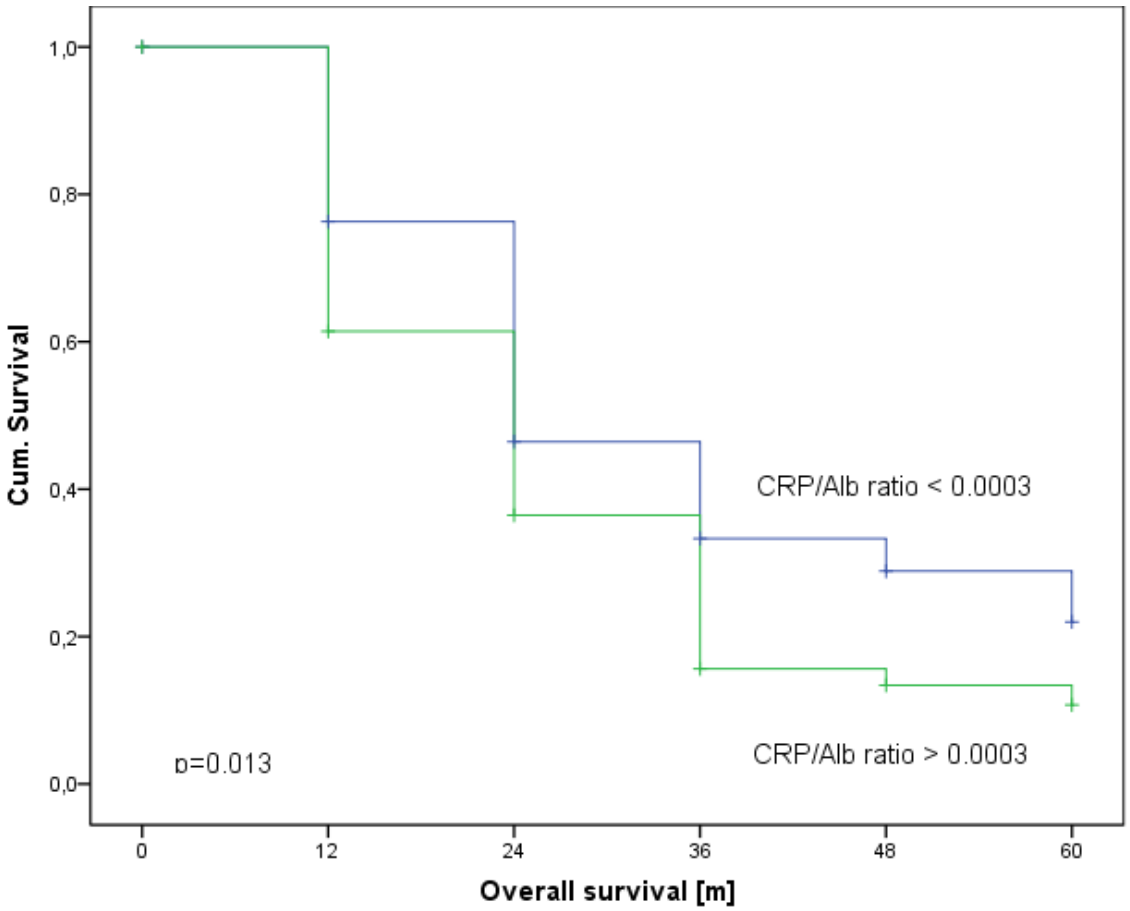


Figure 8: Cumulative survival a) for patients with a serum albumin < 3.5 g/dl (green) vs. patients with a serum albumin > 3.5 g/dl (blue). p= 0.091 b)for patients with a serum CRP > 10 (green) vs. Patients with a serum CRP < 9.77 mg/l. p= 0.103. In comparison to the CRP/alb ratio the two factors alone do not show a significant consequence on the patients follow up time.



Patients at risk					
CRP/Alb ratio < 0.0003	92	49.5	30	21	9
CRP/Alb ratio > 0.0003	32	17.5	7	5	1.5

	1 year survival	5 year survival
CRP/Alb ratio < 0.0003	67%	7%
CRP/Alb ratio > 0.0003	56%	3%

Figure 9: Mortality table of patients with CAR < 0.0003 vs. Patients with CAR < 0.0003. The Patients at risk and 1 year/5 year survival are stated below. Patients with mGPS < 0.0003 have a higher 1 year and 5 year survival rate than patients with a CAR > 0.0003.

The mortality table (figure 9) shows a significant difference between patients with a CRP/Alb ratio < 0.0003 compared to patients with a CRP/Alb ratio > 0.0003. The one-year survival of patients with a CRP/Alb ratio < 0.0003 was 67% whereas patients with a CRP/alb ratio > 0.0003 had a one-year survival of 56%. The five-year survival of patients with CRP/Alb < 0.0003 ratio was 7%, patients with a CRP/Alb ratio > 0.0003 had a 3% chance of surviving five years.

3.4.2 Univariate analysis of clinico-pathological parameters in correlation to the CRP/ Albumin ratio

As shown in Table 15 patients with a CRP/Alb ratio > 0.003 have a significantly shorter overall survival time (15.3 months) than patients with a CRP/Alb ratio < 0.0003 (21.2 months, p=0.021). It was also shown, that patients with a CRP/Alb ratio > 0.0003 have to stay in the hospital about 4 days longer than patients with a CRP/Alb ratio < 0.0003. There was no difference between the two groups regarding age, follow up time, CA 19-9 or CEA.

Table 15: Univariate analysis of clinico-pathological parameters for patients with CRP/alb ratio > 0.003 vs. patients with CRP/alb ratio < 0.003

	CRP/Alb ratio < 0.0003	**CRP/Alb ratio > 0.0003**	**p**	**Sig.**
	mean	**mean**		
Age	65.1	65.1	0.962	-
Survival [m]	21.2	15.3	0.021	*
Follow up [m]	24.9	19.6	0.115	-
Hospital stay [d]	11.3	15.7	0.019	*
CA19-9 [kUI/L]	787.8	2248.9	0.339	-
CEA [µg/L]	4.6	7.9	0.254	-

Using univariate analysis (Table 16) it was shown, that lymph node metastasis is associated with a CRP/Alb ratio > 0.0003. The occurrence of preoperative symptoms, especially jaundice and pancreatitis also correlates with a CRP/Alb ratio > 0.003. There is no correlation of Age>70, female sex, Charlson Index > 2, the occurrence of morbidity after surgery, an ASA > 2, a CA 19-9 > 37 kIU/l, a higher grading, or distant metastasis with a CRP/Alb ratio > 0.0003.

*Table 16: Univariate analysis (chi square test) of clinico-pathological parameters for patients with CRP/Alb ratio <0.0003, and CRP/Alb ratio >0.0003 (p<0.05 *, P<0.01 **, p<0.001 ***) 1: CEA and CA 19-9 values were only available from 149 patients.*

	CRP/Alb ratio < 0.0003 n [%]	**CRP/Alb ratio > 0.0003 n [%]**	**p**	**Sig.**
Age >70	55 [27%]	18 [9%]	0.285	-
Female	67 [33%]	32 [16%]	0.340	-
Charlson Index >2	72 [36%]	40 [20%]	0.026	*
Morbidity	35 [17%]	11 [5%]	0.425	-
ASA > 2	77 [38%]	34 [17%]	0.659	-
CA19-9 > 37 kIU/l[1]	73 [49%]	33 [22%]	0.698	-
CEA > 3.8 µg/l[1]	29 [21%]	18 [13%]	0.050	*
R category 1	58 [35%]	17 [10%]	0.725	-
N category 1	118 [58%]	39 [25%]	0.066	-
Grading 3/4	65 [32%]	26 [13%]	0.825	-
T 3/4	131 [65%]	56 [28%]	0.500	
M category 1	24 [12%]	11 [5%]	0.767	-
UICC IIB/III/IV	114 [56%]	54 [27%]	0.041	*
Preoperative symptoms	81 [42%]	48 [25%]	0.0001	***
Pancreatitis	11 [6%]	11 [6%]	0.019	*
Jaundice	38 [19%]	33 [17%]	0.0001	***
Weight loss	29 [15%]	20 [10%]	0.044	*

3.5 Univariate Analysis of different clinico-pathological parameters using cox regression test

In table 17 univariate analysis of different parameters associated with the follow up time using cox regression analysis is shown. It was found that metastasis, lymph node involvement, a CRP/Alb ratio > 0.0003 and mGPS = 2 are significant independent factors for poor outcome. There was no significant difference for NLR, Albumin level, CRP level, Age, Age > 70, Sex, R-Category, Grading, Charlson Index, an ASA > 2, the occurrence of preoperative symptomatic, CEA level or CA 19-9 level.

*Table 17: Univariate analysis using cox regression of different parameters referred to the overall survival time. (p<0.05 *, P<0.01 **, p<0.001 ***)*

	Median	Odds ratio (95% CI)	p	Significance
NLR > 2		1.438 (0.965 – 2.143)	0.074	-
NLR	3.8	1.020 (0.985 – 1.057)	0.266	-
mGPS 0/1 vs. 2		1.678 (1.006 – 2.825)	0.049	*
CRP/Alb ratio >0.003		1.454 (1.024 – 2.063)	0.036	*
CRP [mg/dl]	15.6	1.003 (1.001 – 1.008)	0.348	-
CRP > 10 mg/dl		1.325 (0.939 – 1.870)	0.109	-
Albumin [g/dl]	4.0	0.923 (0.714 – 1.193)	0.539	-
Albumin < 3.5 g/dl		1.534 (0.924 – 2.546)	0.098	-
CA19-9 [kU/l]	1816.6	1.00 (1.00-1.00)	0.643	-
CA19-9 > 37 kU/l		1.200 (0.791 – 1.821)	0.392	-
CEA [ng/ml]	5.7	1.003 (0.992 – 1.013)	0.600	-
CEA > 3.8 ng/ml		0.873 (0.582 – 1.310)	0.513	-
Age	65.1	1.005 (0.988 – 1.023)	0.553	-
Age >70		0.955 (0.804 – 1.134)	0.955	-
Sex		1.177 (0.847 – 1.636)	0.332	-
N category 1		1.851 (1.191 – 2.875)	0.006	**
R category 1		0.924 (0.641 – 1.332)	0.672	-
M category 1		2.037 (1.357 – 3.059)	0.001	**
UICC IIB/III/IV		2.757 (1.623 – 4.682)	0.0001	***
Charlson Index >2		1.368 (0.975 – 1.919)	0.069	-

Grading 3/4	1.202 (0.866 – 1.670)	0.272	-
T 3/4	1.538 (0.808 – 2.929)	0.190	-
ASA > 2	1.128 (0.809 – 1.572)	0.477	-
Preoperative symptomatic	1.300 (0.907 – 1.863)	0.126	-
Preoperative pancreatitis	1.683 (1.055 – 2.685)	0.029	*

3.6 Multivariate Analysis of different clinico-pathological parameters using cox regression test

Only factors that were significantly correlated with the overall survival time in univariate analysis were considered for multivariate analysis.

Table 18 shows the multivariate analysis of M category 1, a higher grading, CRP/Alb ratio > 0.0003 and the occurence of preoperative pancreatitis. It was shown that CRP/Alb ratio > 0.0003, the Grading, M category and preoperative pancreatitis are significantly correlated in multivariate analysis.

Table 18: Multivariate analysis using cox regression analysis for parameters that showed a significant correlation to the overall survival time in univariate analysis.

	Odds ratio (95% CI)	**p**	**Significance**
Grading 3/4	1.728 (1.225 – 2.439)	0.002	**
Preop. pancreatitis	1.739 (1.073 – 2.819)	0.025	*
M-category 1	1.553 (1.018 – 2.370)	0.041	*
CRP/Alb ratio > 0.0003	1.459 (1.009 – 2.108)	0.045	*

4. Discussion

Pancreatic cancer is still considered to be one of the deadliest cancers. Although it is not very common (4% of all cancer) it is one of the most lethal cases of cancerous illnesses. [1] Radical surgical resection of the tumour remains the only curative option, but is not an equally suitable treatment for all patients alike. The 5-year disease related mortality after resection lies within 75 %. [65]

Until now it has not been fully understood, in which patients a full resection has a profitable outcome or to which factors the long-term survival rate relate to. As a consequence, pre-operative prognostic factors that give indication to survival after resection are of paramount importance, also for further understanding the disease.

Lately, especially factors that include inflammatory aspects have been at the centre of scientific research. This is attributed to the postulated correlation between inflammatory response and the relationship between the tumour and its micro environment.

In this study, examined examples for these inflammatory related predicative factors are NLR, mGPS and the CRP/Alb ratio.

For pancreatic cancer, NLR is one of the best established prognostic factors, as it is easily obtainable from basic laboratory results. This factor, if further assessed, would be ideal for individual risk assessment. Several studies have shown that an elevated NLR is directly linked to reduced survival times for patients in advanced stages of cancer [45, 50, 61, 66-68], as well as patients after curative resection [45, 51, 69]. Nevertheless, patient collectives were often very small and inclusion criteria not comparable. Table 18 summarizes the recent findings regarding a significant influence of NLR for patients after curative resection for pancreatic cancer on survival time.

Table 19: Recent findings regarding a significant influence of NLR for patients after curative resection modified from Stevens et al. 2015 [70] in comparison to the findings of this study

Author	Year	Patient no.	NLR cut-off value	Median survival time (months)
Garcea et al.	2011	74	> 5	undefined
Bhatti et al.	2010	84	> 4	7.1
			< 4	14
Stotz et al.	2013	110	> 5	11.2
			< 5	21.3
Ben Q et al	2016	381	> 2	19.2
			<2	12.4
This study	***2017***	***202***	***> 2***	***18.8***
			< 2	***20.8***

The most described cut-off value is NLR> 5. For this patient collective, we were not able to show that a NLR> 5 is associated with reduced survival in patients with curative resected PDAC. The optimal cut-off value was found to be NLR> 2. This cut-off also has been described by Ben Q et al. for patients after curative resection. [48] The median survival time was only described by Bhatti et al., Stotz et al. and Ben Q et al. The findings of this study correlate with the descriptions of the latter. Since the number of patients included from Bhatti et al. and Stotz et al. were a lot smaller and the type of surgery performed is not specified it has proven difficult to compare the total numbers of all studies. Overall survival times might also depend on the surgeon performing the surgery, the number of patients treated in the facility and whether patients that died within 30 days after the surgery had been excluded from the patient collective. It is

more favourable to compare the survival differences of the two groups these were similar between all studies but this study: Stotz et al. (9 months), Bhatti et al. (7 months), Ben Q et al. (7 months) whereas survival times in this study only differ by 2 months. Not only do these numbers show how short median survival times are, even after curative resection, but also that the individual risk of dying after surgery can be predicted by factoring in the NLR.

Differing from all other studies mentioned, this study could not show a significant relation of NLR by multivariate analysis. Other factors correlated with a NLR > 2 were a Charlson index > 2, preoperative symptoms, especially preoperative pancreatitis and jaundice. Studies showed a correlation of an elevated NLR with hypalbuminaemia, poorer tumour differentiation, increased mGPS [71], advanced UICC stage, T stage and lymph node invasion [48]. We were not able to confirm these findings, but our data correlates with Bhatti et al., who state that there is no statistical difference for lymph node invasion, differentiation and resection margin interrelated to a higher NLR. [51] Wang et al. also proposed, that NLR might be superior to mGPS as a prognostic factor. [71] This study was not able to confirm Wang et al.´s theory since NLR was no significant parameter in univariate or multivariate cox regression analysis. In conclusion, there needs to be further investigation regarding the predictive value of NLR.

The mGPS combines the acute phase protein CRP with hypalbuminaemia and has been the subject of various studies regarding the outcome of cancer patients. For pancreatic cancer, there are several studies regarding mGPS and survival/follow up time, but the conclusion is not unanimous. For patients with a progressed disease, Wu et al., as well as Martin et al. and Stotz et al. showed that a higher mGPS is an independent factor and links to an overall shorter survival. [45, 61, 72] A study that combined all patients with pancreatic cancer has shown that mGPS has no evident prognostic impact for the survival time. [67] For patients after curative resection there

are studies that show a higher mGPS to be an independent factor for survival [55, 73], but also studies that negate a significant difference. [45, 67, 74]

Table 20: Recent findings regarding an influence of mGPS for patients after curative resection in comparison tot he findings of this study

Author	**Year**	**Patient no.**	**mGPS**	**Median survival time (months)**	**p**
Imaoka et al	2016	188	0 1+2	33.9 26.1	Not significant
La Torre et al.	2012	101	0 1 2	37.2 11.5 7.3	0.0001
Stotz et al.	2013	110	0 1+2	undefined	0.585
Jamieson et al.	2011	135	0 1 2	26.7 16.5 13.1	0.0001
This study	***2017***	***202***	***0*** ***1*** ***2***	***21.2*** ***16.6*** ***13.1***	***0.122***

Our study shows a significantly shorter follow up time for patients with a mGPS of 2 compared to patients with a mGPS of 0 and 1 in Kaplan-Meier analysis. In univariate analysis and multivariate analysis, the mGPS has shown no significant impact on follow up or survival time. The overall survival times were 13.1 months for mGPS 2, 16.6 months for mGPS 1 and 21.2 months for mGPS 0. The overall survival times for mGPS 1 and 2 are similar as described by Jamieson et al. but the overall survival time for mGPS 0 in our patient collective was a lot shorter (Table 19) than in any of the other studies described above. This could be the reason for mGPS not showing any significant correlation. Nevertheless, this is consistent with the finding of Stotz et al. and Wu et al. These authors also found no significant correlation between a higher mGPS and the overall survival in multivariate analysis.

We have also found that patients with a higher mGPS have a significantly longer hospital stay than patients with a lower mGPS (mGPS = 0 25.33 days mGPS = 1 27.98

days mGPS = 2 32.84 days). A possible reason for the longer hospital stay is the correlation of a higher mGPS with a Charlson Index > 2 and the occurrence of preoperative symptoms, especially jaundice, as shown in table 18. The level of CEA is also significantly higher in the mGPS = 2 group (12.2 ng/ml) than in the mGPS = 1 (5.63 ng/ml) or mGPS = 0 group (4.79 ng/ml).

The CRP/Alb ratio has previously described as a strong predictive factor for the overall survival in different kinds of cancer, such as oesophageal, liver, lung and gastric cancer. [57-59, 75, 76] For advanced stage pancreatic cancer, the optimal cut-off value was a CRP/alb ratio> 0.54 and that patients with a CRP/Alb ratio > 0.54 showed an overall shorter survival (5.0 vs. 2.9 months), as was found by Wu et al. For patients with curative resection Haruki et al. proposed an optimal cut-off value of 0.03. Patients with a CRP/Alb ratio > 0.03 showed a shorter disease free survival and a decreased survival time (undefined). In our study the optimal cut-off value for the patient collective was 0.0003. In comparison to Wu et al. and Haruki et al. this cut-off value seems overly small, but with the correct conversion factor from mg/l (CRP) to g/dl (albumin) and an average CRP of 15.8 mg/dl, the CRP/alb ratio values are relatively small. Like Wu et. al and Haruki et al. our study showed that patients with a higher CRP/alb. ratio had a 6 months' shorter median survival time (21.2 vs. 15.3 months). It was also confirmed that the CRP/Alb ratio is correlated with worse outcome by cox regression analysis.

The question that arises is whether the CRP/all ratio has any advantage to the CRP values or the Albumin values alone, as it was proposed, that elevated CRP levels > 4.5 mg/l are linked to a poor outcome in patients with advanced stage pancreatic cancer. [77] It was also shown that in comparison to the CRP/alb ratio the two factors alone do not show a significant consequence on the patients follow up time using Kaplan-meier curve. In the cox regression analysis CRP alone was no significant clinico-pathological parameter for patient survival. It can be proposed that the stratification by CRP/alb ratio is superior to serum CRP level alone. Further testing should be done to confirm this hypothesis. Correlated with a CRP/alb ratio > 0.0003 were a longer hospital stay (11.3

vs. 15.7 days), a higher UICC stage, a Charlson Index > 2 and preoperative symptoms, especially jaundice, weight loss and preoperative pancreatitis. Wu et al. showed that an elevated CRP/Alb ratio is associated with an elevated NLR and higher mGPS score. However, they confirmed our findings that there were no significant differences in age, gender, disease stage, tumour location or CA19-9 levels. In our study the CRP/alb ratio is the most promising factor since it was shown to be significant in both univariate and multivariate analysis. In multivariate analysis, it was shown that patients with a CRP/alb ratio > 0.0003, metastasis, preoperative pancreatitis and a higher grading show a poor outcome regarding overall survival times.

Independent factors that correlated with a shorter survival time but the prognostic factors described above were affected lymph nodes, a higher grading, a UICC classification IIB, III or IV and metastasis.

4.1 Limitations of the study

The conducted study is a single centre study with retrospective data collection and all advantages and disadvantages for this style of study are evident. The retrospective analysis does not allow standardized data evaluation since from 258 patients that could have been included in the study, only 191 met all criteria. A prospective study design (e.g. assigning the predictive factors to all patients with pancreatic cancer by the treating physician) would resolve this limitation.

4.2 Conclusion

The predicative value of NLR and mGPS was not confirmed for patients who underwent curative surgery for pancreatic cancer. The results show that the CRP/albumin ratio is an independent prognostic factor for the survival for patients with PDAC after curative pancreatic resection. The Cut-off value has yet to be determined since all conducted studies show different values and more studies maybe also with a perspective study design should be considered.

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