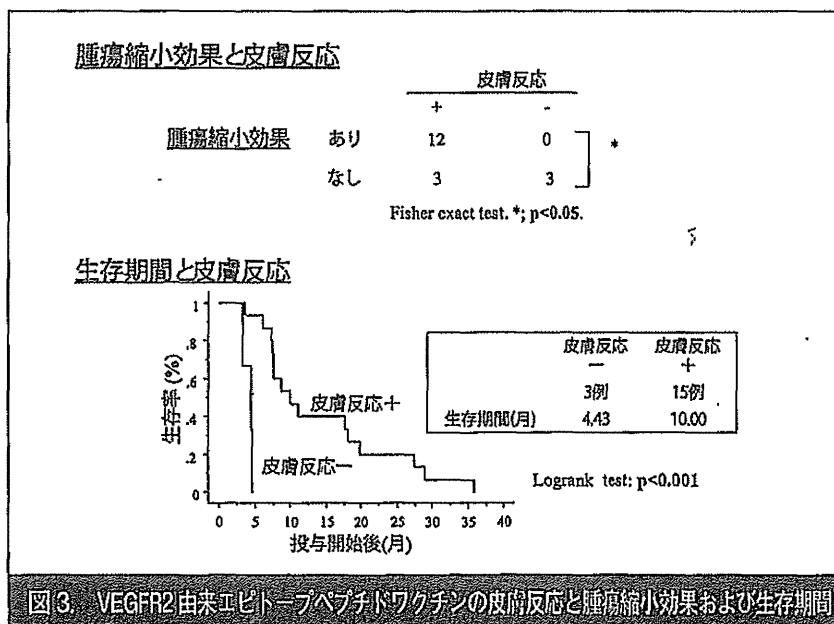


VIII. 免疫反応モニタリング

がんワクチンの作用機序として癌抗原特異的免疫反応を惹起することで抗腫瘍活性を引き起こすと考えられることから、がんワクチンの薬力学的解析として免疫反応をモニタリングすることは極めて重要である。バイオセラピー学会ガイダンスでは、がんペプチドワクチンのモニタリングアッセイ法として、がんペプチドワクチンに対する Delayed type-hypersensitivity(DTH)反応(皮膚反応)、ペプチド特異的細胞傷害試験、ペプチド特異的 IFN- γ ELISPOT アッセイ、ペプチド特異的マルチマーフローサイトメトリー等が推奨される、と明記している。前述の PEGASUS-PC Study は、切除不能進行膵臓癌又は再発膵臓癌の患者 153 例を対象に、VEGFR2 由来のエピトープペプチド：エルパモチドとゲムシタビン併用投与群(実薬群)の安全性及び有効性を確認する目的で、プラセボ(偽薬)とゲムシタビンの投与群(プラセボ群)を対照として行った多施設共同の第 II/III 相二重盲検比較試験である。我々はこの PEGASUS-PC Study を施行する根拠となった第 I 相試験を施行したが²⁰⁾、この試験ではペプチドワクチンの注射部位反応が抗腫瘍効果および生存期間延長と相関することが示され(図3)、皮膚反応と ELISPOT による免疫モニタリングの結果を指標として検証試験のワクチン投与量を決定した。そして、2013 年 1 月の ASCO-GI で報告した検証試験としての PEGASUS-PC Study の結果は、主要評価項目である全生存期間では実薬群とプラセボ群で統計学的有意差は認められなかったものの、注射部位反応によるサブグループ解析を行ったところ、強い皮膚反応(潰瘍)が認められた患者については、生存期間が延長している傾向があることが明らかとなった。特に、注射部位の潰瘍は実薬群においてのみ認められた事象であり、ワクチンにより誘導された特異的 CTL により引き起こされた事象と考えられた。さらに、注射部位反応の有無と生存期間には



ペプチドワクチンによる腫瘍縮小効果および生存期間の延長と投与部位の皮膚反応は、正の相関を認めた。

強い相関が認められ、ワクチン投与部位の皮膚反応は、ワクチン投与による生存期間延長の surrogate marker となりうる可能性が示唆された。現在は肺癌術後補助療法として複数のペプチドワクチンのカクテル製剤に Gemcitabine を併用した医師主導治験を多施設共同で実施しており（平成 23・24・25 年度厚労科研【難病・癌等の疾患分野の医療の実用化研究事業】研究代表者：和歌山県立医科大学外科学第 2 講座山上裕機）、その結果が期待される。また、今後このような臨床研究を進めていく中で、様々なモニタリングアッセイ法の標準化および結果の再現性についてのバリデーションを確実にを行い、がんペプチドワクチン療法の効果が最も期待できる患者群を探索することも重要である。

おわりに

近年のがんペプチドワクチン療法開発の現状と、臨床試験の推進により明らかになってきた、がんワクチンの抗癌剤治療とは異なる作用機序を考慮した開発の方向性について概説した。がんペプチドワクチン療法は創薬化に向けた最終段階にあるが、さらなる発展には、適切なペプチドの開発と選択、免疫逃避機構を打破するアジュバント等の開発、サロゲートマーカーの開発による適切な対象の選択などが重要であり、今後の更なる基礎研究、臨床研究の推進が必要である。

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Atrial fibrillation after esophageal cancer surgery: an analysis of 207 consecutive patients

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Abstract

Purpose The aim of this study was to identify perioperative risk factors that are associated with postoperative atrial fibrillation (AF) and the outcomes of different pharmacological interventions in esophageal cancer patients who underwent transthoracic esophagectomy.

Methods This study included 207 patients who underwent a transthoracic esophagectomy for esophageal cancer resection by a single surgeon from January 1, 2004, through December 31, 2010.

Results Postoperative AF occurred in 19 patients (9.2 %), all of whom received antiarrhythmic drug therapy at the early stage. Antiarrhythmic treatment was effective in 12 cases (63.2 %). In this study, landiolol hydrochloride, an ultrashort-acting β_1 -selective β -blocker, was the first-line therapy for postoperative AF. A multivariate logistic regression analysis showed that postoperative AF was significantly associated with the use of an ileo-colon for reconstruction after esophagectomy ($P = 0.0023$, odds ratios [OR] = 13.6) and with the presence of tachycardia with a heart rate of >100 bpm on postoperative day (POD) 1 ($P = 0.0004$, OR = 18.4).

Conclusions Postoperative AF is associated with the use of a colon conduit for reconstruction after esophagectomy and with tachycardia with a heart rate >100 bpm on POD

1. Identifying patients at high risk for postoperative AF will allow for more direct application of pharmacological methods of prophylaxis.

Keywords Esophageal cancer · Atrial fibrillation · Esophagectomy

Introduction

A transthoracic esophagectomy for the resection of esophageal carcinoma is associated with a high incidence of complications, including postoperative pneumonia, anastomotic leakage and cardiac events. Postoperative atrial fibrillation (AF) is a common arrhythmia after esophagectomy (10–60 %) and is associated with increased morbidity and mortality rates [1–6]. Considerable progress has been made toward decreasing surgical complications, such as anastomotic leakage, because of the standardization of surgical techniques [7]. However, the continued high rate of postoperative AF may be related to the use of extensive lymphadenectomy [8, 9]. Several studies have reported on the use of pharmacological therapies, such as diltiazem, amiodarone and landiolol, to prevent AF after general thoracic surgery, but their effectiveness remains controversial [10–13]. Therefore, the identification of high-risk populations will allow for targeted use, and will resolve questions about the efficacy of the drugs, potentially leading to successful prevention of AF.

Previous studies identified several risk factors predicting the development of AF after esophagectomy, including advanced age, male sex, a history of cardiac disease and a history of chronic obstructive pulmonary disease (COPD) [2, 4, 14]. However, these studies examined only small numbers of patients with esophageal cancer, and the risk

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factors are consequently not clearly understood. Furthermore, these studies included patients who had various surgical procedures, such as the Lewis Tanner operation, transhiatal approach and three-phase lymph node dissection. We routinely perform right transthoracic esophageal resection with two-field (the mediastinum and the abdomen) or three-field (plus bilateral cervix) lymph node dissection and anastomosis with the cervical esophagus in the cervical wound for patients with thoracic esophageal cancer. For these reasons, our study was conducted to identify perioperative risk factors that are associated with postoperative AF, and to assess the outcomes of different pharmacological interventions in esophageal cancer patients who underwent transthoracic esophagectomy.

Patients and methods

Between January 1, 2004, and December 31, 2010, a total of 232 consecutive patients underwent surgery for thoracic esophageal carcinoma at Wakayama Medical University Hospital. This study included 207 patients who underwent transthoracic esophagectomy for esophageal cancer resection by a single surgeon. The patients who underwent esophagectomy with an additional laryngectomy ($n = 2$) or pneumonectomy ($n = 2$) were excluded. Two patients who underwent a nonresective operation (bypass surgery, 1 patient; diagnostic thoracotomy, 1 patient) were also excluded. In addition, 14 patients who underwent palliative esophagectomy were excluded. Five patients who had preoperative AF, defined as a sustained or repetitive arrhythmia documented by electrocardiography (ECG) that required antiarrhythmic therapy [14], were also excluded. Follow-up data were obtained from the database, which included the patients' background, surgical details and tumor characteristics. The tumor invasion (T) and lymph node status (N) were classified by the UICC criteria [15]. Informed consent was obtained from all of the patients in accordance with the guidelines of the Ethics Committee on Human Research of Wakayama Medical University Hospital. Data regarding the patients' age, sex, tumor location, tumor level (TNM stage), cardiac disease, hypertension, preoperative cardiac function test results, preoperative pulmonary function test results, diabetes and treatment with concurrent combined chemotherapy/chemoradiotherapy were analyzed. Patients with conditions such as angina pectoris and previous myocardial infarction were classified as having cardiovascular disease. Poor cardiac function was defined as an ejection fraction $<60\%$, as measured by echocardiography. Patients with abnormal pulmonary function on spirometry (vital capacity ration [%VC] $<70\%$ or forced expiratory volume in 1 s [FEV₁]/forced vital capacity [FVC] $<60\%$) were classified as

having pulmonary disease as a comorbidity [16]. Diabetes mellitus was noted if the patient had a fasting blood glucose concentration >126 mg/dL or was receiving antidiabetic therapy [17]. We administered neoadjuvant chemotherapy with cisplatin and 5-fluorouracil for Stage II–III esophageal cancer. This regimen employed in the Japan Clinical Oncology Group (JCOG) 9907 [18] study is now standard in Japan. In our institute, neoadjuvant chemoradiotherapy (NACRT) has been used to treat localized esophageal carcinoma (cT3–4 tumors). We therefore performed NACRT in the modified JCOG 9906 study with cisplatin and 5-fluorouracil plus concurrent radiotherapy [19].

In our institute, traditional open right transthoracic esophageal resection with two- or three-field lymph node dissection is usually performed for patients with thoracic esophageal cancer. After anterolateral thoracotomy, esophagectomy with regional lymphadenectomy is performed. Our two-field lymph node dissection includes total mediastinal, perigastric and celiac lymphadenectomy. Three-field lymph node dissection adds removal of the lymph nodes in the supraclavicular and cervical paratracheal regions to the two-field approach. In January 2009, we adopted minimally invasive thoracoscopic esophageal resection when the tumor is cT1–2 [20, 21]. In brief, the patient is placed in a prone position, five trocars are placed along the medial edge of the scapula, and thoracoscopic esophagectomy with regional lymphadenectomy is performed. In cases in which a patient has lower third thoracic esophageal cancer with poor cardiac function or has had a previous right thoracotomy, we perform left transthoracic esophageal resections. If the lesion is located in the middle or upper third of the thorax, we use hand-assisted laparoscopic surgery for mobilization of the stomach and abdominal lymph node dissection and gastric tube formation [22].

A gastric conduit through the retrosternal route or through the posterior mediastinum is usually used to construct the anastomosis with the cervical esophagus. In patients with previous gastrectomy or concomitant gastric cancer, the right ileo-colon is used. The esophageal anastomosis is then established in an end-to-side fashion in the cervical wound.

All patients underwent perioperative respiratory rehabilitation, and 125 mg of methylprednisolone was administered intravenously at the beginning of the thoracotomy and again at the end of the surgery [23, 24]. All patients were admitted to the intensive care unit immediately after the operation. All patients began standing and walking on postoperative day (POD)1. Epidural analgesia was used routinely for postoperative pain management for 1 week. All patients having a postoperative cardiac diagnosis by ECG remained under continuous monitoring for at least 72 h after surgery.

In this study, postoperative complications were analyzed according to the Clavien–Dindo classification and the thoracic morbidity and mortality (TM&M) system [25, 26]. In this study, complications higher than Grade II were regarded as clinically significant postoperative complications. Grade II refers to any complication that requires pharmacological treatment or minor intervention only; Grade III means any complication that requires surgical, radiological or endoscopic intervention or multiple therapies (Grade IIIa indicates that intervention does not require general anesthesia; Grade IIIb indicates that intervention requires general anesthesia) and Grade IV indicates any complication requiring intensive care unit management and life support. Surgical mortality (Clavien–Dindo classification Grade V) included in-hospital deaths within 30 days after surgery.

Postoperative AF was defined as an absent P wave before the QRS complex, with irregular ventricular rhythm on the rhythm strips [1, 14]. Leakage at the anastomosis site was determined by the leakage of contrast medium by upper gastrointestinal series after surgery. An intra-abdominal abscess (including bile leakage) was defined as intra-abdominal fluid collection, identified by ultrasonography or computed tomography (CT), with positive cultures. The diagnosis of postoperative pneumonia was made via CT and an elevated white blood cell count and serum C-reactive protein (CRP) level. Respiratory failure was defined as the need for intubation and mechanical ventilation in patients. The diagnosis of postoperative pneumothorax and diaphragmatic hernia was made via chest CT. Postoperative deterioration of liver function was defined by a serum aspartate aminotransferase level more than two times the upper limit of the normal level within 14 days after the operation. The diagnosis of postoperative vocal cord paralysis was made via bronchoscopy, which is a routine examination in our group (POD1).

The StatView 5.0 software package (Abacus Concepts, Inc., Berkeley, CA) was used for all statistical analyses. Quantitative results are expressed as medians and ranges. A statistical analysis was performed using Fisher's test. A *P* value <0.05 was considered to be significant. The univariate and multivariate logistic regression analyses were performed to identify risk factors influencing the development of postoperative AF. Risk factors with a univariate *P* < 0.10 were included in the multivariate analysis. Risk factors with a multivariate *P* < 0.05 were defined as independent risk factors.

Results

Table 1 shows the detailed characteristics of the 207 patients, including 167 males and 40 females, with a

median age of 66 years. The tumor was located in the upper third of the thorax in 16 patients (7.7 %), middle third of the thorax in 151 patients (72.9 %) and lower third of the thorax in 40 patients (19.3 %), and the median tumor size was 39 mm. The primary tumors were squamous cell carcinoma (193; 93.2 %), adenocarcinoma (10; 4.8 %) and others (4; 1.9 %). Twenty-five (12.1 %), 34 (16.4 %), 54 (26.1 %), 55 (26.6 %) and 39 (18.8 %) patients had TNM Stage 0, I, II, III and IV, respectively.

Table 2 shows the surgical data. A total of 171 patients (82.6 %) underwent an open right transthoracic esophageal resection. Twenty-eight patients (13.5 %) received a minimally invasive thoracoscopic esophageal resection [21]. Eight patients underwent a left transthoracic esophageal resection. One hundred thirteen patients received a radical three-field lymphadenectomy (total mediastinum, abdomen and cervix), and 88 patients received a two-field lymphadenectomy (total mediastinum and abdomen). After esophagectomy, the stomach was used for reconstruction in 182 patients, the ileo-colon was used in 24 patients and the

Table 1 Clinicopathological features of the patients (*n* = 207)

Age, years (median, range)	66 (43–85)
Sex (male/female)	167/40
Tumor location (Ut/Mt/Lt)	16/151/40
Tumor size, mm (median, range)	39 (3–90)
Pathology (SCC/adenocarcinoma/other)	193/10/4
Depth of invasion ^a (T0/Tis/T1/T2/T3/T4)	2/6/83/35/79/2
TNM stage ^a (0/I/II/III/IV)	25/34/54/55/39
NAC (%)	53 (25.6)
NACRT (%)	14 (6.8)

Ut upper third of the thorax, Mt middle third of the thorax, Lt lower third of the thorax, SCC squamous cell carcinoma, NAC neoadjuvant chemotherapy, NACRT neoadjuvant chemoradiotherapy

^a UICC TNM 7th edition

Table 2 Surgical data (*n* = 207)

Approach (right thoracotomy/thoracoscope/left thoracotomy)	171/28/8
Lymph node dissection (3-field/2-field/1-field) ^a	113/88/6
Conduit (stomach/colon/jejunum)	182/24/1
Route of reconstruction (retrosternal/posterior mediastinum)	148/59
Median length of operation, min (range)	525 (310–776)
Median blood loss, mL (range)	437 (45–3,100)
Blood transfusion (%)	54 (26.1)
Curative resection ^b (%)	192 (92.8)

^a Three-field indicates bilateral cervical regions, the mediastinal space and the abdomen; two-field indicates the mediastinum and the abdomen and one-field indicates the abdomen and the middle/low mediastinum

^b UICC TNM R0

jejunum was used in one patient. The median duration of the operation was 525 min, and the median blood loss was 437 mL.

The details of the postoperative complications for esophagectomy (more than Grade II morbidity) are listed in Table 3. One or more complications were experienced by 61 patients (29.5 %). AF and pneumonia, classified as Grade II, only required medical therapy (e.g. beta-blockers for AF, or antibiotics for pneumonia). Seventeen patients with lateral vocal cord paralysis were followed through swallowing rehabilitation until recovery. Five patients with bilateral vocal cord paralysis required tracheostomy. Anastomotic leakage was observed in eight patients (3.9 %), six with minor leaks and two with leaks requiring additional drainages. Three patients with respiratory failure required 1–14 days of ventilation and tracheostomy early in the series, and subsequently required 1 month to recover. Diaphragmatic hernias occurred in two patients after esophagectomy with gastric pull-up (one patient with a retrosternal gastric tube, one patient with an intrathoracic gastric tube). These two patients underwent diaphragmatic hernia repair in open surgery. In our series of 207 patients who underwent esophagectomy, no surgical mortality occurred.

Table 3 Postoperative complications ($n = 207$)

Complications	No. (%)	Clavien–Dindo classification ^a (n)		
		Grade II	Grade IIIa	Grade IIIb
Any	61 (29.5)			
Atrial fibrillation	19 (9.2)	19		
Vocal cord paralysis ^b	22 (10.6)	17	5	
Pneumonia	12 (5.8)	12		
Anastomotic leakage	8 (3.9)	6	2	
Pneumothorax	6 (2.9)	6		
Wound infection	5 (2.4)	5		
Respiratory failure	3 (1.4)			3
Chylothorax	2 (1.0)	2		
Cervical lymphatic leakage	2 (1.0)	2		
Enteritis	2 (1.0)	2		
Diaphragmatic hernia	2 (1.0)			2
Deterioration of liver function	1 (0.5)	1		
Bile leakage	1 (0.5)		1	
Intra-abdominal abscess	1 (0.5)		1	
Mortality	0 (0)			

^a Surgical complications were classified into five categories by the Clavien–Dindo classification

^b Including transient paralysis

Other complications related to the esophagectomy (more than Grade II morbidity) affected 63.2 % of the patients who had postoperative AF (12/19) compared with 16.0 % of the patients without AF (30/188) ($P < 0.0001$, Table 4). We found that postoperative complications were more common in patients with postoperative AF.

Table 5 shows the details of the patients with postoperative AF. All patients were male, and had a median age of 69 years. In all cases, the postoperative AF occurred within 48 h after surgery. In 12 of the 19 patients (63.2 %), AF was found after patients were up and walking postoperatively. The median duration of postoperative AF was 3.7 days (range 0.5–14 days). All 19 patients received antiarrhythmic drug therapy in the early stage, and 12 patients (63.2 %) responded positively. Successful treatment was defined as a heart rhythm change to a sinus rhythm within 72 h of the start of treatment. In our institute, landiolol hydrochloride, an ultrashort-acting β_1 -selective β -blocker has been used as the first-line therapy against postoperative AF since 2002 [12].

The univariate and multivariate analyses were performed to identify risk factors for postoperative AF. Table 6 shows the results of the analysis of the 31 variables that were univariately examined as potential risk factors for the 19 patients with postoperative AF vs the 188 patients without postoperative AF. Nine of the 31 factors differed significantly between these groups ($P < 0.10$). Of the preoperative factors, patients having hypertension ($P = 0.0003$) and having other arrhythmia ($P = 0.0064$) were found to be significant. In terms of the intraoperative factors, ileo-colon use for reconstruction ($P < 0.0001$), reconstruction through the retrosternal route ($P = 0.0870$) and a long operation ($P = 0.0058$) were selected as significant predictors. Among the various postoperative factors, dopamine use ($P = 0.0484$), the onset of other complications ($P < 0.0001$), tachycardia ($P < 0.0001$) and fever ($P = 0.0041$) were selected. The multivariate logistic regression analysis indicated that postoperative AF was significantly associated with the use an ileo-colon for reconstruction after esophagectomy ($P = 0.0023$) and the presence of tachycardia with a heart rate of >100 bpm on POD1 ($P = 0.0004$), with odds ratios of 13.6 (95 % confidence interval [CI], 2.5–72.4) and 18.4 (95 % CI, 3.7–92.0), respectively.

Table 4 Correlation between the onset of postoperative atrial fibrillation and other complications in patients after esophagectomy ($n = 207$)

Other complications	Atrial fibrillation		
	Yes ($n = 19$)	No ($n = 188$)	P value
Yes ($n = 42$)	12	30	<0.0001
No ($n = 165$)	7	158	

We found that postoperative AF was significantly associated with the use of a colon conduit for reconstruction and with tachycardia on POD1 (Table 6). Therefore, we examined the incidence of postoperative AF in patients with these factors. As shown in Table 7, the incidence of postoperative AF in patients with both colon conduit use for reconstructions after esophagectomy and those who had tachycardia with a rate >100 bpm on POD1 was 100 % (4/4), while the incidence of postoperative AF in patients without these two factors was only 2.4 % (4/168).

Discussion

Major pulmonary complications and surgical sepsis are common morbidities in patients with AF after esophagectomy [6]. The association of postoperative AF with mortality has also been documented after lung surgery [27] and after major noncardiac operations [14]. In the present

study, postoperative complications were also frequently observed in patients with AF.

We speculate that AF after esophagectomy is caused by an inflammatory response following surgical trauma to the sympathovagal nerve fibers supplying the heart [2, 28, 29]. It has been reported that advanced age and a history of cardiac disease are predisposing factors for postoperative AF [6]. Ma et al. [2] reported that AF was associated with postoperative hypoxia, a history of COPD, thoracic–gastric dilatation, an age older than 65 years, male sex and a history of cardiac disease. Stippelet al [30] reported that an elevated body temperature was the most important predisposing factor for AF. Interestingly, Hou et al. [1] described that an elevated level of perioperative N terminal (NT)-pro B-type natriuretic peptide (BNP) is an independent predictor of AF. Thus, previous studies have shown different results.

We found that the use of colonic interposition for esophageal replacement after esophagectomy was a predictor of postoperative AF. This association has not been

Table 5 Summary of patients with postoperative atrial fibrillation

Patient no.	Age	Sex	Onset of an AF	Situation at the onset	Duration of AF (days)	Drugs	Other complications
1	72	M	POD2	Resting	0.5	Digoxin	None
2	68	M	POD2	Resting	0.5	Digoxin	Pneumonia
3	71	M	POD2	Resting	2	Digoxin	None
4	68	M	POD2	Resting	4	Digoxin	Pneumothorax
5	85	M	POD2	After walking	6	Digoxin Landiolol Verapamil	Enterocolitis
6	77	M	POD2	After walking	10	Landiolol Pilsicainide Verapamil	Respiratory failure
7	71	M	POD1	After walking	4	Digoxin Landiolol Verapamil	Pneumonia
8	68	M	POD1	Resting	1	Landiolol	Vocal cord paralysis
9	52	M	POD2	Resting	0.5	Pilsicainide	Vocal cord paralysis
10	64	M	POD2	After walking	1	Landiolol	None
11	72	M	POD2	After walking	3	Landiolol Disopyramide	None
12	76	M	POD2	After walking	2	Landiolol	Anastomotic leakage
13	75	M	POD2	After walking	14	Landiolol	Anastomotic leakage Intra-abdominal abscess
14	67	M	POD2	Resting	3	Landiolol	None
15	65	M	POD2	After walking	6	Pilsicainide	Vocal cord paralysis
16	71	M	POD1	After walking	2	Landiolol	None
17	65	M	POD1	After walking	2	Landiolol	Pneumothorax
18	59	M	POD1	After walking	7	Landiolol	None
19	62	M	POD2	After walking	2	Pilsicainide	Vocal cord paralysis

AF atrial fibrillation, POD postoperative day, M male

Table 6 Results of the univariate and multivariate analyses of risk factors influencing the postoperative atrial fibrillation

Risk factors	Categories	Univariate analysis	Multivariate analysis	
		<i>P</i> value	<i>P</i> value	Odds ratio (95 % CI)
Preoperative factors				
Sex	Male	0.9668		
	Female			
Age (years)	≥70	0.2932		
	<70			
BMI (kg/m ²)	≥25	0.9666		
	<25			
Cancer location	Ut	0.9793		
	Mt/Lt			
NAC	Yes	0.5326		
	No			
NACRT	Yes	0.4979		
	No			
History of cardiovascular disease	Yes	0.1864		
	No			
History of hypertension	Yes	0.0003	0.0648	3.660 (0.923–14.510)
	No			
History of pulmonary disease	Yes	0.2573		
	No			
History of diabetes mellitus	Yes	0.7009		
	No			
Ejection fraction (%)	<60	0.5659		
	≥60			
R(L)BBB, PVC or AV block	Yes	0.0064	0.1410	3.289 (0.674–16.057)
	No			
Intraoperative factors				
Approach	Thoracotomy	0.1068		
	Thoracoscope			
Lymphadenectomy	3-Field	0.1099		
	2-Field			
Conduit	Colon	<0.0001	0.0023	13.580 (2.546–72.426)
	Gastric tube/jejunum			
Route of reconstruction	Retrosternal	0.0870	0.3277	2.727 (0.366–20.338)
	Posterior mediastinum			
Thoracic duct resection	Yes	0.9786		
	No			
Duration of operation (min)	≥600	0.0058	0.6799	1.384 (0.295–6.484)
	<600			
Blood loss (mL)	≥500	0.1917		
	<500			
Blood transfusion	Yes	0.2674		
	No			
Curative resection ^a	Yes	0.7278		
	No			
Postoperative factors				
Dopamine use	Yes	0.0484	0.6966	0.746 (0.171–3.249)
	No			

Table 6 continued

Risk factors	Categories	Univariate analysis	Multivariate analysis	
		<i>P</i> value	<i>P</i> value	Odds ratio (95 % CI)
Sivelestat use	Yes	0.3785		
	No			
Complications other than AF	Yes	<0.0001	0.0516	4.920 (1.924–16.710)
	No			
Sinus heart rate in POD 1 (bpm)	≥100	<0.0001	0.0004	18.401 (3.680–92.003)
	<100			
Hemoglobin in POD1 (g/dL)	<8	0.9764		
	≥8			
WBC on POD 1 (/ μ L)	≥10,000	0.2379		
	<10,000			
CRP on POD 1 (mg/dL)	≥10	0.8663		
	<10			
PaO ₂ on POD 1 (mm Hg)	<100	0.5042		
	≥100			
Highest CVP on POD 1 (mm Hg)	<5	0.6214		
	≥5			
Highest fever on POD1 (°C)	≥37	0.0041	0.1261	3.053 (0.730–12.757)
	<37			

CI confidence interval, BMI body mass index, NAC neoadjuvant chemotherapy, NACRT neoadjuvant chemoradiotherapy, *U_t* upper third of the thorax, *M_t* middle third of the thorax, *L_t* lower third of the thorax, *R(L)BBB* right(left) bundle branch block, *PVC* premature ventricular contraction, *AV block* atrioventricular block, *AF* atrial fibrillation, *POD* postoperative day, *WBC* white blood cell, *CRP* C-reactive protein, *CVP* central venous pressure

^a UICC TNM R0

Table 7 Incidence of postoperative atrial fibrillation in patients with two risk factors, colon conduit use for reconstructions and sinus tachycardia with a rate >100 bpm on POD1

Risk categories ^a	AF cases	(%)
Risk 0		
Without colon conduit, HR < 100 bpm	4/168	2.4
Risk 1–1		
Without colon conduit, HR ≥ 100 bpm	6/15	40.0
Risk 1–2		
With colon conduit, HR < 100 bpm	5/20	25.0
Risk 2		
With colon conduit, HR ≥ 100 bpm	4/4	100.0

POD postoperative day, HR heart rate, AF atrial fibrillation

^a Risk 0 indicates the patients without colon conduit use for reconstruction after esophagectomy and with a heart rate <100 bpm on POD1. Risk 1–1 indicates the patients without colon conduit use for reconstruction but with tachycardia with a heart rate >100 bpm. Risk 1–2 indicates the patients with colon conduit use for reconstruction who had a heart rate <100 bpm. Risk 2 indicates the patients with both colon conduit use for reconstruction and tachycardia

demonstrated in the previous studies. In general, transthoracic esophagectomy produces an excessive inflammatory response, which may lead to the development of systemic

inflammatory response syndrome and postoperative morbidities [24]. In particular, colonic reconstruction after esophagectomy is a more complex procedure, with increased morbidity compared with gastric transposition [31]. The blood loss is greater and the length of the operation is longer in the colonic reconstruction group, reflecting the complexity of the operation [31]. Therefore, it is suggested that esophagectomy with reconstruction using a colonic conduit is accompanied by much greater surgical stress, which might translate to a high incidence of postoperative AF.

In this study, sinus tachycardia with a rate >100 bpm on POD1 was the most significant risk factor for postoperative AF. The peak incidence of postoperative AF was on POD1 or 2, which is consistent with the findings of previous studies [2, 4]. A previous report in patients undergoing pulmonary surgery also showed similar results [14]. In our institute, esophageal cancer patients are consistently up and walking on POD1 or 2 after esophagectomy, and as a result, the greatest incidence of AF was found after walking. We suspect that the increases in heart rate during walking may have triggered the AF. We previously found that a perioperative physiotherapy and pulmonary rehabilitation program improves the exercise capacity and early

ambulation in patients undergoing esophagectomy [23]. Therefore, we consider early mobilization to be essential for patients that have undergone esophagectomy; however, it is also important to control the heart rate on POD1 and 2 in order to prevent AF after esophagectomy.

Intraoperative fluid therapy decisions may also influence the postoperative AF. Our surgical team and anesthesiologist kept the infusion rates between 6 and 8 mL/kg/h during esophagectomy, and the intraoperative urine output was kept between 0.5 and 1 mL/kg/h. Therefore, we consider that the water balance during the operation had no influence on the postoperative AF in our series of patients.

Prophylactic therapy may be performed for high-risk groups, including patients who undergo esophagectomy with reconstruction using a colon conduit and/or patients with sinus tachycardia after esophagectomy, to prevent the occurrence of postoperative AF. Indeed, the incidence of postoperative AF in patients with colon conduit use for reconstructions and tachycardia on POD1 was 100 %. The current commonly cited guidelines do not provide a specific recommendation for anticoagulation in the postoperative period for general thoracic surgeries [32]. Early attention to heart rate control and possible conversion back to normal sinus rhythm is a well-accepted principle of current patient care [32]. We consider landiolol hydrochloride to be a first-line therapy against postoperative AF [12]. Landiolol is a drug which acts as a highly cardioselective, ultrashort-acting β_1 -selective β -blocker. It is often used as an anti-arrhythmic agent in Japan. Because of its extremely short half-life in the blood (<4 min), landiolol is outstanding in terms of its immediate efficacy and adjustability. Recent randomized controlled studies using landiolol have reported significant reductions in AF after cardiac surgery compared with placebo [12]. Another randomized controlled study clearly demonstrated that the mortality and the perioperative incidence of cardiovascular events could be reduced by the use of β -blockers in patients who underwent major noncardiac surgery [33]. Therefore, we may reduce not only the incidence of AF, but also other postoperative complications after esophagectomy, with the use of landiolol. While several medications have been used for postoperative AF prophylaxis without risk discrimination, a better understanding of the mechanisms responsible for postoperative AF could help in the design of novel prophylactic or therapeutic measures targeting those who are at the greatest risk. Clinical trials of the prophylactic use of landiolol to prevent postoperative AF are now planned in patients at high risk who undergo transthoracic esophagectomy.

Conflict of interest None.

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A new prognostic score for the survival of patients with esophageal squamous cell carcinoma

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Abstract

Purpose Recent studies have shown that the modified Glasgow Prognostic Score (mGPS), which is an inflammation-based prognostic score, is useful as a prognostic index for some cancer cases. The purpose of this study was to create a prognostic scoring system for patients with esophageal squamous cell carcinoma (ESCC) that was more independent and sensitive than the mGPS.

Methods One hundred sixty-eight patients who had undergone esophagectomy for ESCC were included in the study. The new mGPS (NmGPS) was calculated based on the following cutoff values: CRP >0.75 mg/dL indicated NmGPS 1 or 2, depending on the absence or presence of hypoalbuminemia (<3.5 g/dL); and CRP ≤0.75 mg/dL indicated NmGPS 0. We also performed an analysis based on cutoff values of 0.5 and 0.25 mg/dL for CRP.

Results Only the NmGPS with a cutoff CRP value of 0.5 mg/dL was able to divide into three independent patient groups in the survival curves. In the multivariate analyses, a NmGPS (CRP cutoff; 0.5 mg/dL) of 2 was a more significant independent prognostic factor (HR 4.437, 95 % CI 2.000–9.844, $p = 0.0002$) than a mGPS of 2 (HR 2.726, 95 % CI 1.021–7.112, $p = 0.0449$).

Conclusions The new prognostic score NmGPS (CRP cutoff; 0.5 mg/dL) was more independent and sensitive than the mGPS for patients with ESCC.

Keywords Esophageal squamous cell carcinoma · Inflammation-based prognostic score · Glasgow Prognostic Score (GPS)

Abbreviations

GPS	Glasgow Prognostic Score
mGPS	Modified Glasgow Prognostic Score
NmGPS	New modified Glasgow Prognostic Score
CRP	C-reactive protein
ESCC	Esophageal squamous cell carcinoma
AIC	Akaike information criterion
HR	Hazard ratio
CI	Confidence interval
SIR	Systemic inflammatory response
IL-6	Interleukin-6

Introduction

Esophageal cancer is the eighth-most common cancer worldwide and the sixth-most common cause of cancer death [1]. The predominant histological subtype of esophageal cancer is squamous cell carcinoma (SCC), which comprises about 80 % of all esophageal cancers worldwide [2]. In Asian countries, especially Japan, China and Iran, about 90 % of esophageal cancers are SCC [3]. On the other hand, in the United States and other Western countries, about 50 % of esophageal cancers are adenocarcinomas [4]. Because there are important biological differences between esophageal cancers in Asian and Western countries, a prognostic model that takes into account the predominance of SCC in Asian countries is necessary for deciding on a postoperative strategy that will prolong survival. Markers predicting the malignant potential of tumors and the prognosis of patients with esophageal

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squamous cell carcinoma (ESCC) would be extremely useful.

Previous reports have shown that systemic inflammation, indicated by an elevated level of serum C-reactive protein (CRP), strongly influenced the prognosis of patients with gastrointestinal carcinomas, including gastro-esophageal cancer [5] and colorectal cancer [6]. Moreover, the combination of an elevated serum CRP level and hypoalbuminemia is considered to be an important prognostic factor [7]. Indeed, the Glasgow prognostic score (GPS), which is based on the serum CRP level and hypoalbuminemia, has been demonstrated to be an indicator for the prognosis of patients with neoplasms of the digestive tract, including colorectal cancer [8], gastric cancer [9] and pancreatic cancer [10]. The GPS seemed to be a simple prognostic indicator for human tumors and was calculated easily as follows: a score of 0 for normal C-reactive protein and albumin levels, 1 for either an abnormal C-reactive protein or abnormal albumin level and 2 for abnormal C-reactive protein and abnormal albumin levels. Because hypoalbuminemia alone was not associated with reduced survival [11], recent reports have demonstrated the superior usefulness of the modified GPS (mGPS) for prognostication of the mortality in patients with colorectal cancer [12], pancreatic cancer [13] or gastric cancer [14].

However, some of the studies using the GPS or mGPS have had various problems. For example, since the number of patients with GPS 1 or 2 (mGPS 1 or 2) was significantly smaller than the number of patients with a 0 score [15], the GPS or mGPS may have an obvious bias. Moreover, there was no significant difference found between the survival curves of patients with GPS 1 and those with GPS 0 or 2 [9, 16]. In addition, neither the GPS nor mGPS was able to be separated into three independent patient groups with each GPS (mGPS) according to the survival curves. Therefore, the GPS and mGPS may be considered insufficient for prognostication. A new version of the GPS is therefore necessary to improve the prognostication. We herein investigated three new CRP cutoff values to establish a new mGPS (NmGPS) for esophageal cancer, especially SCC. Then, we compared the mGPS with the NmGPS with respect to the clinicopathological features and prognostic significance. The purpose of this study was to create a prognostic scoring system for patients with potentially resectable ESCC that is more sensitive than the mGPS.

Materials and methods

Patients, blood samples and laboratory measurements

One hundred sixty-eight patients with esophageal cancer who had been treated by esophagectomy and lymph node dissection from January 2003 through December 2008 at Wakayama

Medical University Hospital (WMUH) were evaluated. The patients who had other malignant tumors, who had other inflammatory diseases causing elevated levels of serum CRP, who died immediately after surgery (within 30 days) or who died because of non-cancer-related causes were excluded from this study. Patients with R1 or R2 status were included to evaluate aggressive tumor biology. All blood samples were collected and tested for the serum CRP and albumin levels just before surgery. The scores were evaluated as follows: First, we assessed the mGPS, as previously described by several groups [12–14]. Patients with an elevated level of CRP (>1.0 mg/dL) were assigned a mGPS of 1 or 2, depending on the absence or presence of hypoalbuminemia (<3.5 g/dL), and patients who did not have an elevated level of CRP (≤ 1.0 mg/dL) were assigned a mGPS of 0. We assessed the values of our new version of the mGPS (NmGPS) using three CRP cutoff values: 0.75, 0.5 and 0.25 mg/dL. Initially, patients with an elevated level of CRP (>0.75 mg/dL) were assigned a NmGPS (CRP cutoff; 0.75 mg/dL) of 1 or 2, depending on the absence or presence of hypoalbuminemia (<3.5 g/dL). Patients without an elevated level of CRP (≤ 0.75 mg/dL) were assigned a NmGPS (CRP cutoff; 0.75 mg/dL) of 0. Alternate NmGPS values were assigned based on CRP cutoffs of 0.5 mg/dL and 0.25 mg/dL. We selected the most appropriate new mGPS from these three models and then compared the mGPS with the NmGPS with respect to their relationships with the clinicopathological features and their prognostic significance. The primary objective was to decide which CRP value was the most specific for cancer-specific survival. This study was approved by the Ethical Committee on Clinical Investigation of WMUH. Informed consent was obtained from all participating patients preoperatively.

The pathological classification of the primary tumor, the degree of lymph node involvement and the presence of organ metastasis were determined according to the TNM classification system (7th edition of the cancer staging manual of the American Joint Committee on Cancer [17]).

Surgical procedure

All patients underwent radical esophagectomy with a two- or three-field lymph node dissection via a cervicothoraco-abdominal approach. A gastric conduit through the retrosternal rout or through the posterior mediastinum was usually used to reconstruct the anastomosis with the cervical esophagus. However, in patients, who had undergone a prior gastrectomy or who had concomitant gastric cancer, the right ileocolon was used.

Neoadjuvant therapy and adjuvant therapy

Beginning in 2005, we administered neoadjuvant chemotherapy for patients with clinical lymph node metastases,

and neoadjuvant chemoradiotherapy for patients with clinical T4 lesions. We performed esophagectomy about 1 month after the end of neoadjuvant therapy, when the inflammatory response due to the neoadjuvant therapy would have disappeared. Nineteen patients received neoadjuvant therapy. Among them, 12 received chemotherapy consisting of 5-fluorouracil/cisplatin, and seven received radiotherapy with chemotherapy. Seventy-seven patients received postoperative adjuvant therapy. Among them, 74 with pathological lymph node metastases received chemotherapy consisting of 5-fluorouracil/cisplatin or 5-fluorouracil/cisplatin/docetaxel, and three with residual tumors received radiotherapy with chemotherapy.

Patient follow-up

All patients were followed up at regular intervals after discharge from our hospital. This included blood tests for tumor markers, such as carcinoembryonic antigen (CEA), SCC and cytokeratin 19 fragment antigen 21-1 (CY-FRA21-1) every 3 months, and a follow-up CT scan and an endoscopic examination every 6 months. As of the writing of this manuscript, the median follow-up time for surviving patients was 39 (range 5–99) months. None of the patients were lost to follow-up.

Statistical analysis

The data are presented as prevalences or medians. The Chi-square test was used to test for correlations between the clinicopathological parameters and prognostic scores. The cancer-specific survival curves were estimated by the Kaplan–Meier method, and the prognostic factors were assessed by the log-rank test and a Cox proportional hazards model for the univariate and multivariate analyses. The results are presented as hazard ratios (HRs) with 95 % confidence intervals (CIs). Moreover, we used the Akaike information criterion (AIC) to identify the best statistical model [18]. The AIC was defined as: $AIC = -2 \log \text{maximum likelihood} + 2 \times (\text{the number of parameters in the model})$. A smaller AIC value indicates a more desirable model for predicting the outcome. The statistical analyses were performed with the SPSS Version 21.0 software program (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered to be statistically significant.

Results

The study included 168 patients with histological subtype ESCC. The clinicopathological features are summarized in Table 1. The study population included 135 males and 33 females aged 47–85 years (median age 67 years).

The 3-year cancer-specific survival rates of the patients with mGPS 0, 1 and 2 were 81.7, 42.8 and 31.3 %, respectively. There were statistically significant differences between the survival of patients with mGPS 0 and 1 ($p = 0.0002$), and between patients with mGPS 0 and 2 ($p < 0.0001$). There was no significant difference between the survival rates of patients with mGPS 1 and 2 ($p = 0.1860$) (Fig. 1a). The 3-year cancer-specific survival rates of patients with NmGPS (CRP cutoff; 0.75 mg/dL) 0, 1 and 2 were 82.3, 43.6 and 28.8 %, respectively. There were statistically significant differences between the survival rates of patients with NmGPS (CRP cutoff; 0.75 mg/dL) 0 and 1 ($p = 0.0001$), and between patients with NmGPS (CRP cutoff; 0.75 mg/dL) 0 and 2 ($p < 0.0001$). There was no significant difference between the survival rates of patients with NmGPS (CRP cutoff; 0.75 mg/dL) 1 and 2 ($p = 0.1171$) (Fig. 1b). The 3-year cancer-specific survival rates of patients with NmGPS (CRP cutoff; 0.5 mg/dL) 0, 1 and 2 were 86.5, 51.0 and 27.8 %, respectively. There were statistically significant differences between the survival rates of patients with NmGPS (CRP cutoff; 0.5 mg/dL) 0 and 1 ($p < 0.0001$), between patients with NmGPS (CRP cutoff; 0.5 mg/dL) 0 and 2 ($p < 0.0001$) and between patients with NmGPS (CRP

Table 1 Clinicopathological features of the patients

Sex ratio, male/female	135/33
Median age (range), years	67 (47–85)
mGPS 0/1/2, <i>n</i>	137/19/12
NmGPS (CRP cutoff; 0.75 mg/dL) 0/1/2, <i>n</i>	135/20/13
NmGPS (CRP cutoff; 0.5 mg/dL) 0/1/2, <i>n</i>	121/26/21
NmGPS (CRP cutoff; 0.25 mg/dL) 0/1/2, <i>n</i>	88/56/24
Histological type, <i>n</i>	
Differentiated/undifferentiated	117/51
Lymphatic invasion 0/1, 2, 3	66/102
Venous invasion 0/1, 2, 3	86/82
Median maximum tumor size (range), mm	40 (5–100)
Two-/three-field lymph node dissection, <i>n</i>	62/106
Depth of tumor invasion T0/1/2/3/4, <i>n</i>	5/59/22/74/8
Lymph node metastasis N0/1/2/3, <i>n</i>	68/25/32/43
Distant metastasis M0/1, <i>n</i>	166/2
TMN stage 0/IA/IB/IIA/IB/IIIA/IIIB/IIIC/IV, <i>n</i>	6/31/8/18/13/25/15/50/2
Residual tumor R0/1, 2, <i>n</i>	159/9
Neoadjuvant therapy yes/no, <i>n</i>	19/149
Chemotherapy/CRT, <i>n</i>	12/7
Adjuvant therapy yes/no, <i>n</i>	77/91
Chemotherapy/CRT, <i>n</i>	74/3

mGPS modified Glasgow Prognostic Score, NmGPS new modified Glasgow Prognostic Score, T tumor, N node, M metastasis, CRT chemoradiotherapy

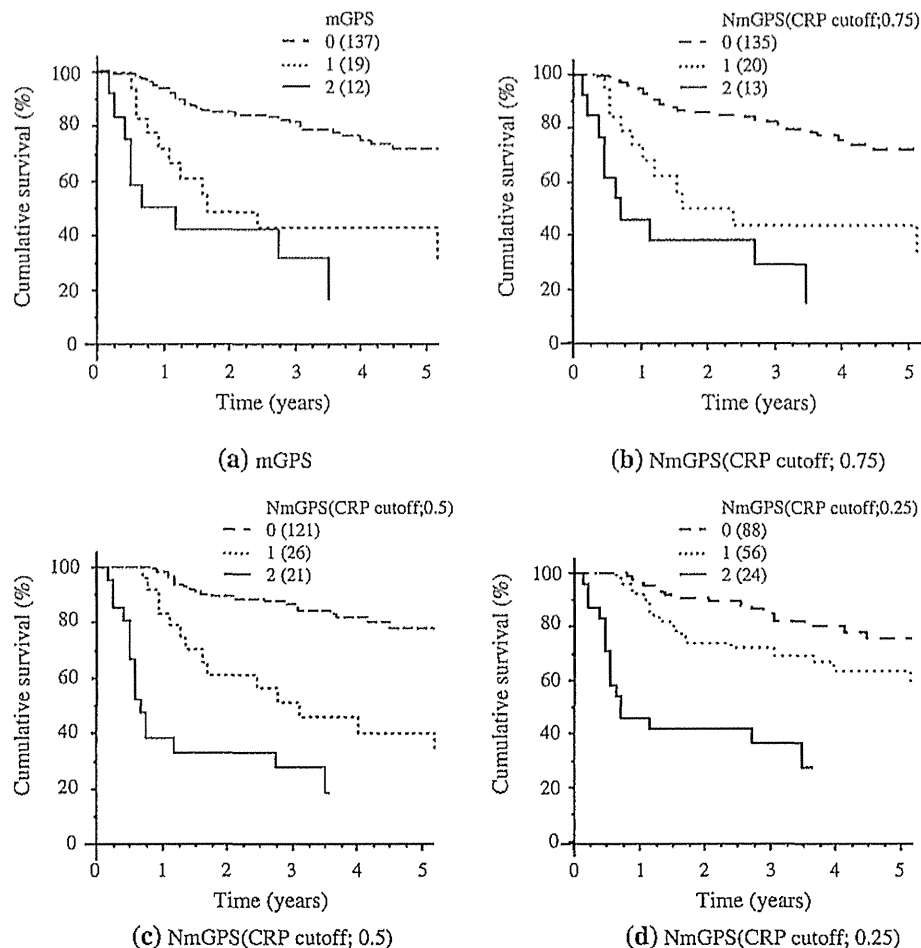


Fig. 1 a The cancer-specific survival curves based on the modified Glasgow Prognostic Score (mGPS). The 3-year cancer-specific survival rates of patients with a mGPS of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 81.7, 42.8 and 31.3 %, respectively. There were statistically significant differences between the survival rates of patients with a mGPS of 0 and 1 ($p = 0.0002$), and between patients with a mGPS of 0 and 2 ($p < 0.0001$). There was no significant difference between the survival rates of patients with a mGPS of 1 and 2 ($p = 0.1860$). **b** The cancer-specific survival curves based on the new modified Glasgow Prognostic Score (NmGPS [CRP cutoff; 0.75 mg/dL]). The 3-year cancer-specific survival rates of patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 82.3, 43.6 and 28.8 %, respectively. There were statistically significant differences between the survival rates of patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 0 and 1 ($p = 0.0001$), and between patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 0 and 2 ($p < 0.0001$). There was no significant difference between the survival rates of patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 1 and 2 ($p = 0.1171$). **c** The

cutoff; 0.5 mg/dL) 1 and 2 ($p = 0.0099$) (Fig. 1c). The 3-year cancer-specific survival rates of patients with NmGPS (CRP cutoff; 0.25 mg/dL) 0, 1 and 2 were 85.1, 71.9 and 36.5 %, respectively. There were statistically significant differences between the survival of patients with NmGPS (CRP cutoff; 0.25 mg/dL) 0 and 2 ($p < 0.0001$)

cancer-specific survival curves based on the new modified Glasgow Prognostic Score (NmGPS [CRP cutoff; 0.5 mg/dL]). The 3-year cancer-specific survival rates of patients with a NmGPS (CRP cutoff; 0.5 mg/dL) of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 86.5, 51.0 and 27.8 %, respectively. There were statistically significant differences between the survival rate of patients with a NmGPS (CRP cutoff; 0.5 mg/dL) of 0 and 1 ($p < 0.0001$), of 0 and 2 ($p < 0.0001$), and between patients with a NmGPS (CRP cutoff; 0.5 mg/dL) of 1 and 2 ($p = 0.0099$). **d** The cancer-specific survival curves based on the new modified Glasgow Prognostic Score (NmGPS [CRP cutoff; 0.25 mg/dL]). The 3-year cancer-specific survival rates of patients with a NmGPS (CRP cutoff; 0.25 mg/dL) of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 85.1, 71.9 and 36.5 %, respectively. There were statistically significant differences between the survival rates of patients with a NmGPS (CRP cutoff; 0.25 mg/dL) of 0 and 2 ($p < 0.0001$), and between patients with a NmGPS (CRP cutoff; 0.25 mg/dL) of 1 and 2 ($p < 0.0001$), but not between those with a NmGPS (CRP cutoff; 0.25 mg/dL) of 0 and 1 ($p = 0.0685$)

and between patients with NmGPS (CRP cutoff; 0.25 mg/dL) 1 and 2 ($p < 0.0001$), but not between patients with NmGPS (CRP cutoff; 0.25 mg/dL) 0 and 1 ($p = 0.0685$) (Fig. 1d). Only NmGPS (CRP cutoff; 0.5 mg/dL) was able to divide into three independent patient groups in the survival curves.

Table 2 The Akaike information criterion (AIC) for the prognostic scoring systems

Prognostic score	AIC
mGPS	1059.0
NmGPS (CRP cutoff; 0.75 mg/dL)	1055.8
NmGPS (CRP cutoff; 0.5 mg/dL)	1044.9
NmGPS (CRP cutoff; 0.25 mg/dL)	1054.1

mGPS modified Glasgow Prognostic Score, *NmGPS* new modified Glasgow Prognostic Score

The AIC of the mGPS, NmGPS (CRP cutoff; 0.75 mg/dL), NmGPS (CRP cutoff; 0.5 mg/dL) and NmGPS (CRP cutoff; 0.25 mg/dL) were 1059.0, 1055.8, 1044.9 and 1054.1, respectively (Table 2). The NmGPS (CRP cutoff; 0.5 mg/dL) showed a smaller AIC than the mGPS and other NmGPS, so we selected the NmGPS (CRP cutoff; 0.5 mg/dL) as the optimal prognostic score and compared the mGPS with the NmGPS (CRP cutoff; 0.5 mg/dL) with respect to the clinicopathological features and prognostic

Table 3 The relationships between the mGPS and the clinicopathological features

Variable	mGPS 0 (<i>n</i> = 137)	mGPS 1 (<i>n</i> = 19)	mGPS 2 (<i>n</i> = 12)	<i>p</i>
Age, years				0.6128
≤65	66 (48.2 %)	7 (36.8 %)	5 (41.7 %)	
>65	71 (51.8 %)	12 (63.2 %)	7 (58.3 %)	
Sex				0.5084
Male	108 (78.8 %)	16 (84.2 %)	11 (91.7 %)	
Female	29 (21.2 %)	3 (15.8 %)	1 (8.3 %)	
Depth of tumor invasion				<0.0001
T0/1/2	81 (59.1 %)	3 (15.8 %)	2 (16.7 %)	
T3/4	56 (40.9 %)	16 (84.2 %)	10 (83.3 %)	
Lymph node metastasis				0.0101
N0	61 (44.5 %)	7 (36.8 %)	0 (0 %)	
N1/2/3	76 (55.5 %)	12 (63.2 %)	12 (100 %)	
Distant metastasis				<0.0001
M0	137(100 %)	19 (100 %)	10 (83.3 %)	
M1	0	0	2 (16.7 %)	
Histological type				0.2552
Differentiated	99 (72.3 %)	14 (73.7 %)	6 (50.0 %)	
Undifferentiated	38 (27.7 %)	5 (26.3 %)	6 (50.0 %)	
Lymphatic invasion				0.4047
0	57 (41.6 %)	6 (31.6 %)	3 (25.0 %)	
1, 2, 3	80 (58.4 %)	13 (68.4 %)	9 (75.0 %)	
Venous invasion				0.0043
0	77 (56.2 %)	3 (15.8 %)	6 (50.0 %)	
1, 2, 3	60 (43.8 %)	16 (84.2 %)	6 (50.0 %)	
Maximum tumor size, mm				0.0004
≤40	80 (58.4 %)	4 (21.1 %)	2 (16.7 %)	
>40	57 (41.6 %)	15 (78.9 %)	10 (83.3 %)	
Lymph node dissection				0.2819
Two fields	47 (34.3 %)	10 (52.6 %)	5 (41.7 %)	
Three fields	90 (65.7 %)	9 (47.4 %)	7 (58.3 %)	
Neoadjuvant therapy				0.0436
Yes	13 (9.5 %)	2 (10.5 %)	4 (33.3 %)	
No	124 (90.5 %)	17 (89.5 %)	8 (66.7 %)	
Adjuvant therapy				0.6440
Yes	62 (45.3 %)	8 (42.1 %)	7 (58.3 %)	
No	75 (54.7 %)	11 (57.9 %)	5 (41.7 %)	
TNM stage				0.0013
0, I, II	70 (51.1 %)	6 (31.6 %)	0	
III, IV	67 (48.9 %)	13 (68.4 %)	12 (100 %)	
Residual tumor				<0.0001
R0	136 (99.3 %)	16 (84.2 %)	7 (58.3 %)	
R1/2	1 (0.7 %)	3 (15.8 %)	5 (41.7 %)	

mGPS modified Glasgow Prognostic Score, *T* tumor, *N* node, *M* metastasis, *R* residual tumor

Table 4 The univariate prognostic factors for esophageal cancer (including the mGPS)

Variable	<i>p</i>	HR	95 % CI
Sex (male)	0.4597	1.312	0.639–2.694
Age (>65 years)	0.1343	1.550	0.873–2.751
mGPS (2)	<0.0001	5.664	2.717–11.809
Depth of tumor invasion (T3, 4)	<0.0001	3.801	2.057–7.025
Lymph node metastasis			
N1	0.0215	3.064	1.179–7.962
N2	0.0165	3.476	1.256–9.625
N3	<0.0001	10.200	4.573–22.739
Distant metastasis (M1)	<0.0001	3.745	2.165–6.476
Histological type (undifferentiated)	0.4363	0.765	0.390–1.501
Lymphatic invasion (1, 2, 3)	0.0047	2.541	1.332–4.850
Venous invasion (1, 2, 3)	0.0021	2.453	1.383–4.351
Tumor size (>40 mm)	0.0013	2.750	1.484–5.098
Lymph node dissection (three fields)	0.6601	1.142	0.632–2.064
Neoadjuvant therapy	0.5469	1.302	0.552–3.069
Adjuvant therapy	0.0020	2.468	1.392–4.374
Residual tumor (R1, 2)	<0.0001	17.248	7.826–38.016

mGPS modified Glasgow Prognostic Score, HR hazard ratio, CI confidence interval, T tumor, N node, M metastasis

Table 5 The multivariate prognostic factors for esophageal cancer (including the mGPS)

Variable	<i>p</i>	HR	95 % CI
mGPS (2)	0.0449	2.726	1.021–7.112
Depth of tumor invasion (T3, 4)	0.1884	1.718	0.767–3.848
Lymph node metastasis			
N1	0.1074	2.620	0.811–8.464
N2	0.0625	2.729	0.949–7.847
N3	0.0178	3.964	1.269–12.383
Distant metastasis (M1)	0.2256	1.569	0.757–3.250
Lymphatic invasion (1, 2, 3)	0.3861	0.711	0.329–1.538
Venous invasion (1, 2, 3)	0.0464	2.274	1.016–5.912
Tumor size (>40 mm)	0.5015	1.293	0.611–2.737
Adjuvant therapy	0.2073	1.589	0.773–3.266
Residual tumor (R1, 2)	0.0152	3.605	1.280–10.149

mGPS modified Glasgow Prognostic Score, HR hazard ratio, CI confidence interval, T tumor, N node, M metastasis

significance. The relationships between mGPS and clinicopathological features are summarized in Table 3.

Statistically significant associations were detected between the prognostic scores and the tumor depth ($p < 0.0001$), lymph node metastasis ($p = 0.0101$), distant metastasis ($p < 0.0001$), venous invasion ($p = 0.0043$), maximum tumor size ($p = 0.0004$), neoadjuvant therapy ($p = 0.0436$), advanced stage ($p = 0.0013$) and residual

tumor R1/2 ($p < 0.0001$). The univariate analysis demonstrated that a mGPS of 2 ($p < 0.0001$), the depth of tumor invasion ($p < 0.0001$), lymph node metastasis (N1) ($p = 0.0215$), N2 ($p = 0.0165$), N3 ($p < 0.0001$), distant metastasis ($p < 0.0001$), lymphatic invasion ($p = 0.0047$), venous invasion ($p = 0.0021$), the maximum tumor size ($p = 0.0013$), neoadjuvant therapy ($p = 0.0020$) and R1/2 status ($p < 0.0001$) were associated with a worse prognosis (Table 4). The multivariate analysis demonstrated that a mGPS of 2 ($p = 0.0449$), lymph node metastasis (N3) ($p = 0.0178$), venous invasion ($p = 0.0464$) and R1/2 tumors ($p = 0.0152$) were independently associated with a worse prognosis (Table 5).

The relationships between the NmGPS (CRP cutoff; 0.5 mg/dL) and clinicopathological features are summarized in Table 6. Similar statistically significant differences were detected regarding the depth of tumor invasion ($p < 0.0001$), lymph node metastasis ($p = 0.0008$), distant metastasis ($p = 0.0008$), venous invasion ($p = 0.0015$), maximum tumor size ($p < 0.0001$), neoadjuvant therapy ($p = 0.0007$), adjuvant therapy ($p = 0.0166$), advanced stage ($p < 0.0001$) and R1/2 status ($p < 0.0001$). In the univariate analysis, a NmGPS (CRP cutoff; 0.5 mg/dL) of 2 was associated with a worse prognosis ($p < 0.0001$) (Table 7). The multivariate analysis demonstrated that a NmGPS (CRP cutoff; 0.5 mg/dL) of 2 ($p = 0.0002$), lymph node metastasis (N3) ($p = 0.0201$), venous invasion ($p = 0.0190$) and R1/2 status ($p = 0.0209$) were independently associated with a worse prognosis (Table 8).

Discussion

We evaluated the associations between the serum CRP and serum albumin levels with the clinicopathological features and cancer-specific survival of patients with ESCC. Moreover, we established a prognostic scoring system more sensitive than the mGPS, with a lower CRP cutoff value. This study is the first to evaluate a new, optimal mGPS, and to compare it with the mGPS for patients with ESCC. In fact, the NmGPS (CRP cutoff; 0.5 mg/dL) could indicate more aggressive tumor biology, in terms of the depth of tumor invasion, presence of lymph node metastasis, distant metastasis, venous invasion, the maximum tumor size, advanced stage and R1/2 status. The number of patients with a mGPS of 2 was very small (7.1 %), in contrast to the number of patients with a mGPS 0 or 1. Moreover, there were no significant differences between the survival curves of patients with a mGPS of 1 and 2. Therefore, the mGPS was unable to be separated into three independent patient groups. On the other hand, when patients were classified based on the NmGPS (CRP cutoff; 0.5 mg/dL), there were significant differences between