ANTICANCER RESEARCH *38*: 1097-1104 (2018)
doi:10.21873/anticanres.12328

Fibrinogen Levels Are Associated with Lymph Node Involvement and Overall Survival in Gastric Cancer Patients

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Abstract. *Background/Aim: Combination of perioperative chemotherapy with gastrectomy with D2 lymphadenectomy improves long-term survival in patients with gastric cancer. The aim of this study was to investigate the predictive value of preoperative levels of CRP, albumin, fibrinogen, neutrophil-to-lymphocyte ratio and routinely used tumor markers (CEA, CA 19-9, CA 72-4) for lymph node involvement. Materials and Methods: This retrospective study was conducted in 136 patients who underwent surgery between 2007 and 2015. Bivariable and multivariable analyses were performed in order to identify important characteristics associated with the risk of lymph node involvement. Kaplan-Meier survival curves and log-rank tests were used to compare overall survival. Results: Lymph node involvement was significantly affected by preoperative fibrinogen (p=0.008) and albumin (p=0.023). Poor clinical condition, T and N staging and fibrinogen level above 3.5 g/l were significantly associated with worse overall survival. Conclusion: Preoperative fibrinogen and albumin levels are significantly associated with lymphoid metastases in patients with gastric cancer.*

Until 2008, gastric cancer (GC) was the fourth most common cancer in the world (1). According to Globocan 2012 there were approximately 952,000 new cases of GC in the world, accounting for 6.8% of all diagnosed cancers and making this cancer the 5th most common malignancy globally (2). Moreover, it is the third leading cause of death in both sexes accounting for 8.8% of the total deaths from cancer (3).

In spite of advancements in chemotherapy and local control of GC, prognosis remains poor, mainly because of the advancement of the disease at the time of diagnosis. Approximately 50% patients in western countries have metastases at the time of diagnosis, and from those without metastatic disease only 50% are eligible for gastric resection (4). The five-year relative survival in Europe varies between 10.6% and 24.0% (5).

Patients at the 4th stage will most likely not benefit from aggressive therapy approaches. Therefore, it is important to increase detection of earlier stages thereby permitting patient-specific tailoring of therapy and improved outcomes. Promising therapeutic procedure for patients without presence of distant metastases is the combination of chemotherapy applied before and after radical resection with D2 lymphadenectomy. The benefit is achieved by reducing tumor size and by stabilization of lymph node (LN) involvement (6, 7). British MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) and French ACCORD (French Action Clinique Coordonnées en Cancérologie Digestive) prospective trials have proved that this therapeutic approach results in higher five-year survival rate and progression-free survival (8, 9).

The decision on whether perioperative chemotherapy is indicated is based primarily on TNM staging. Given that preoperative (clinical) cTNM staging is mainly determined by imaging methods with limited sensitivity, it would be beneficial to specify preoperative staging with the use of available laboratory biomarkers in order to identify patients with unsuspected LN involvement among the patients with (clinical) cN0 stage. There are many monitored markers that could possibly specify pre-treatment cTNM staging. The list of

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Key Words: Fibrinogen, gastric cancer, perioperative chemotherapy, TNM, lymphoid metastasis.

conventional tumor markers used for patients with GC includes carcinoembryonic antigen (CEA), and carbohydrate antigens 19-9 (CA 19-9) and 72-4 (CA 72-4) (10). It is a well-known fact that the serum levels of CEA, CA 19-9 and CA 72-4 are elevated in patients with GC; however, their clinical utility remains uncertain. It has been reported that CEA and CA 19-9 are associated with LN involvement (11, 12) and that CA 72-4 is the most sensitive and specific marker for the GC patients, whose positivity is associated with advanced tumor stage, LN and distant metastases (13-19).

With increasing evidence that systemic inflammatory response plays an important role in carcinogenesis and tumor progression (20-22), more attention is being paid to identifying and monitoring inflammation-based markers, acute-phase proteins, and to associated changes in differential blood count (23, 24). Pre-treatment albumin (ALB) has been observed as a significant prognostic factor in GC (25-27) and elevated C-reactive protein (CRP) to be associated with progressive disease or an advanced stage and a worse survival (28). Another promising available biomarker seems to be a neutrophil-to-lymphocyte ratio (NLR) (29-31) which reflects inflammation status and is associated with clinical stage and survival in patients with GC (32).

Fibrinogen (FBG) is another acute-phase protein and important clotting factor primarily produced by hepatic cells, being evaluated for its potential to improve diagnostic accuracy and management approaches. In addition to its role in blood coagulation, cell adhesion and the inflammatory response (33), FBG at higher levels has been shown to promote cancer cell growth, progression and metastasis (34-38). Furthermore, hypercoagulation status indicated by high FBG level has been reported to be associated with tumor progression, metastasis, and survival in patients with GC (36, 37).

The primary objective of this study was therefore to investigate the predictive value of preoperative levels of CRP, ALB, FBG, NLR and other routinely used tumor markers (CEA, CA 19-9, CA 72-4) for LN metastases detection prior to surgery. A secondary aim was to explore their association with long-term outcomes.

Materials and Methods

Data were extracted retrospectively from the database at the Saint Elizabeth Cancer Institute in Slovakia. All records of patients who underwent surgery for GC between 01 January 2007 and 31 December 2015, and entered a routine follow-up protocol were retrieved and screened for eligibility. The inclusion criteria for this study were as follows: 1) age >21 years; 2) histologically confirmed gastric cancer of any stage. Exclusion criteria: Gastrointestinal Stromal Tumors and lymphomas. Finally, a total of 136 patients with GC were included in the study. Clinicopathological stage of all patients was classified according to TNM classification 2010 (39). Patients with localized and potentially resectable disease (T1-4 N0-3 M0) underwent radical surgery. Presence of distant metastases, peritoneal dissemination and lymph node involvement except locoregional gastric lymph nodes [LN stations 1-12 and 14v according to Japanese classification (40)] precludes the possibility of radical surgery or perioperative chemotherapy, moving these patients into the group scheduled for palliative treatment or explorative laparoscopy to clarify disease staging. Patients who did not survive the immediate postoperative period, *i.e.* within 30 days after surgery, were excluded.

Outcomes of main interest – LN involvement in the attempt to model the observed data as a function of patients' preoperative characteristics. Secondary outcomes – deaths from any cause occurring during the follow-up – were considered beginning on day of surgery and continuing until patients deceased. Survivors and patients censored for loss to follow-up (*e.g.* transfer of care), were considered beginning on day of surgery and continuing until the last recorded visit or until 01 December 2016 (the end of study).

Laboratory measurements. Preoperative plasma FBG, serum ALB, CRP, CEA, CA 19-9, CA 72-4 and complete blood count were examined using standard laboratory protocols in samples taken from patients preprandially a day to three weeks prior to surgery.

Ethical standards. This study was approved by the Medical Ethics Committee of St. Elizabeth Cancer Institute.

Statistical analysis. Data were summarized as means with the respective standard deviations (SD) for continuous variables or as medians and ranges for data showing departures from normality. Categorical variables are presented as counts and relative frequencies. Bivariable and multivariable analyses were performed in order to identify statistically and clinically important characteristics associated with the risk of LN involvement. The variables selected for the final logistic regression model are quoted with corresponding ORs along with the respective 95% confidence intervals (95%CI). Kaplan-Meier survival curves and log-rank tests were used to compare overall survival (OS) grouped by variables of interest.

All reported *p*-values were two sided, and significance level was set at $p<0.05$. StatsDirect 3.0.161 software (Stats Direct Ltd., Cheshire, UK) and Statistica 13 software (Dell-StatSoft, Inc. Tulsa, OK, US) were used.

Results

From a total of 136 patients with GC, 79 (58.1%) were males and 57 (41.9%) were females. No patient died in the immediate postoperative period (<30 days). Patients' demographic and clinicopathological characteristics grouped by the outcome are summarized in Table I. Lymph node involvement was present in 83 (61.0%) patients and absent in 37 (27.2%) patients. The extent of LN involvement of nine patients scheduled for explorative surgery, and three patients scheduled for palliative surgery who underwent surgical exploration only, was classified as presumably present. Those 16 patients were characterized by a more aggressive clinical presentation and poorer outcome (Figure 1, lower left). Characteristics of patients with examined LN involvement are summarized in Table II. Medians of the pre-treatment levels of seven markers are listed as well. Among the characteristics, higher FBG and lower ALB levels were significantly associated with LN involvement, and higher

Table I. *Clinical characteristics of 136 patients with gastric cancer treated between January 2007 and December 2015 – grouped by outcome.*

Patients' characteristics Number (%)*		Total n=136 (100%)	Dead n=71 (100%)	Survived n=65 (100%)	*p*-Value
Age (years)	Mean±SD	64.3±10.74	64.6±11.48	64.0±9.95	0.737
Gender	Male	79 (58.1)	39 (61.5)	40 (54.9)	0.4885
	Female	57 (41.9)	32 (38.5)	25 (45.1)	
Histological type	Intestinal	51 (37.5)	19 (26.8)	32 (49.2)	0.0024
	Mixed	7 (5.1)	2 (2.8)	5 (7.7)	
	Diffuse	78 (57.4)	50 (70.4)	28 (43.1)	
NACT	Yes	17 (12.5)	5 (7.0)	12 (18.5)	0.0501
	No	119 (87.5)	66 (93.0)	53 (81.5)	
Surgery	Radical	110 (80.9)	46 (64.8)	64 (98.5)	<0.0001
	Palliative	17 (12.5)	16 (22.5)	1 (1.5)	
	Explorative LP**	9 (6.6)	9 (12.7)	0 (0.0)	
Stage	T1	24 (17.6)	5 (7.0)	19 (29.2)	<<0.0001
	T2	22 (16.2)	5 (7.0)	17 (26.1)	
	T3	45 (33.1)	20 (28.2)	25 (38.5)	
	T4	45 (33.1)	41 (57.8)	4 (6.2)	
LN involvement	Presumably present***	16 (11.8)	15 (21.1)	1 (1.5)	0.0005
	Present	83 (61.0)	46 (64.8)	37 (56.9)	
	Absent	37 (27.2)	10 (14.1)	27 (41.6)	

(%)*: Expressed as percentage of the column total, if applicable; *p*-Value: probability value; SD: standard deviation; NACT: neoadjuvant therapy; **: patients scheduled for explorative laparotomy; LN: lymph node; ***: patients who underwent surgical exploration and did not undergo resection or palliative surgery.

CEA and CA 72-4 levels were likely associated with LN involvement. Consequently, these characteristics were examined in the course of developing a multivariable model of LN involvement.

Nodal status assessment in gastric cancer. In order to investigate the separate and joint effects of the selected explanatory variables, and to find a simple method of predicting LN involvement on the basis of symptoms, tests, and personal characteristics of patients we performed bivariable and multivariable logistic regressions. Patients that had a probability of LN involvement ≥0.5 were classified as having LN metastases, and patients with a probability <0.5 were classified as not having LN metastases. We kept in mind that the extent of LN involvement remained actually unknown for 16 (11.8%) patients, who underwent explorative surgery because of a more advanced disease at the time of initial diagnosis, that could introduce confounding factors (peritoneal carcinomatosis, liver metastases, *etc.*) in the estimates of regression coefficients, and subsequently in the interpretation of the obtained findings. To examine the potential bias introduced by the group having had explorative surgery, we developed several models for a subgroup of 120 patients who underwent radical or palliative surgery and compared the estimates obtained for the whole sample of 136 patients with the patients on explorative surgery coded as (presumably) positive for LN involvement. We examined all preoperatively known characteristics, and constructed models from the variables that contributed to the LN involvement prediction with the achieved level of significance in bivariable analysis of $p=0.2$ at least. We were focused on the variable of interest FBG (in g/L), the potential confounders, age (in years) and sex (coded as 1=male, 0=female), as well as on the clinical and laboratory characteristics such as histology (coded as 1=diffuse or mixed type, 0=intestinal), NACT (coded as 1=yes, 0=no), and the NLR (the absolute ratio values).

We found out that FBG levels itself were not able to sufficiently discriminate between LN positive and negative patients. Moreover, the AUC for NLR in the bivariable was not significantly different from the null model AUC of 50%. The AUC amounted to 62% ($p<0.01$), and OR=1.80 with 95%CI=1.06-3.06 ($p=0.03$). The classification efficiency of FBG as a single variable in the model was not sufficient to make a reliable prediction. However, its inclusion in the multivariable model as an additional covariate significantly increased the classification performance of the model as evaluated by the deviance likelihood ratio Chi-square statistics and by the AUC.

Further, the variable NACT, and/or the NLR did not significantly discriminate between LN positive and negative patients. Neither the variable NACT, nor NLR improved the predictive performance of multivariable models.

The final model was therefore composed of four variables known before surgery which proved to be most efficient in predicting the LN involvement. In no case the excluding

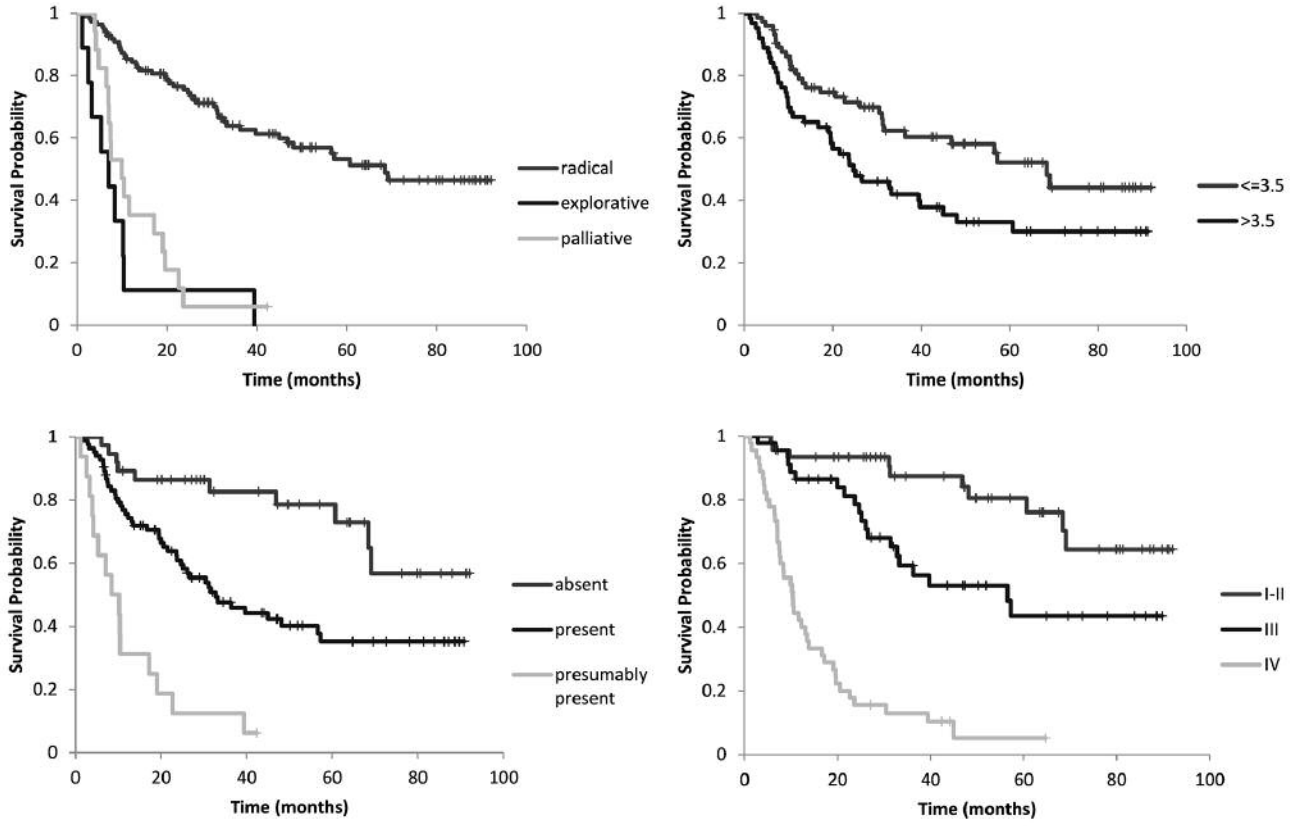

Figure 1. *Kaplan-Meier curves for overall survival in patients with gastric cancer grouped by type of surgery (upper left, overall log rank test: p<0.0001, explorative vs. palliative: non-significant), lymph node status (lower left, with inoperable patients scored as "presumably present" LN involvement, overall log rank test: p<0.0001), preoperative FBG (upper right, levels of 3.5 g/L or above were considered elevated, p=0.0142), and postoperative TNM staging (lower right, overall log rank test: p<0.0001).*

explorative surgeries significantly altered regression estimates of the selected explanatory variables (data not shown). Here, we present the model for the subgroup of patients with radical or palliative surgery (Table III) as a justified and more conceptually correct model. The overall diagnostic performance of the model at the probability cut-off=0.5: sensitivity=89.2%; specificity=18.9%; +ve predictive value=71.2%; -ve predictive value=43.8%; predictive value despite -ve test=56.2%; correctly classified=67.5%; and area under ROC curve=72.8%. The specificity of the model can be increased (at the expense of decreasing sensitivity) by increasing the probability cut-off for classification (c.f. Legend of Table III).

Survival analysis. In order to study the association of patients' characteristics known after surgery on OS we performed a Kaplan-Meier analysis. Visual inspection of differences in unadjusted curves (Figure 1, upper left) confirmed the assumption that the risk of death was highest in the group of inoperable patients and the patients with palliative surgery (the median survival time of 7.1 with 95%CI from 3.3 to 8.5, and 9.9 months with 95%CI=7.0-17.2, respectively). The median survival time of the patients with curative surgery was significantly higher (68.4, 95%CI=45.0-69.1).

The overall five-year survival was 41.6% (95%CI=31.9-51.0). The median survival times in groups by type of surgery were 68.4 months (95%CI=44.9-69.1) for radical surgery, 10.0 months (95%CI=7.0 to 17.2) for palliative surgery and 7.1 months (95%CI=3.3-8.5) for explorative laparoscopy/laparotomy group (the overall log rank test: $p<0.0001$). For patients with fibrinogen levels above 3.5 g/L the 5-year survival were 30.0% with 95%CI=30.0-18.0, and for patients with fibrinogen levels below or equal 3.5 g/L the 5-year survival was 52.1% with 95%CI=64.7-37.7). This difference was significant ($p=0.0142$, Figure 1, upper right). Patients with unknown LN status due to lack of sampling had significantly worse survival than patients with examined LN, even with those having metastases in LN (Figure 1, lower left; $p<0.0001$). These patients were therefore categorized as presumably having present LN involvement.

Table II. *Clinical and laboratory characteristics of 120 patients with gastric cancer treated by radical or palliative surgery between January 2007 and December 2015 – grouped by lymph node status.*

Patients' characteristics Number (%)*		Total n=120 (100%)	LN positive n=83 (100%)	LN negative n=37 (100%)	*p*-Value
Age (years)	Mean±SD	64.6±10.31	64.3±10.30	65.2±10.45	0.675
Gender	Male	72 (60.0)	56 (67.5)	16 (43.24)	0.016
	Female	48 (40.0)	27 (32.5)	21 (56.76)	
Fibrinogen	Mean±SD	3.55±1.01	3.68±1.13	3.25±0.60	0.008
Neu/Ly Ratio	Median (Range)	2.64 (0.77-8.50)	2.54 (0.77-8.50)	2.78 (0.87-8.22)	0.777
CRP	Median (Range)	4.0 (1.0-169.8)	2.25 (1.0-14.8)	4.1 (1.0-169.8)	0.297
Albumin	Mean±SD	37.65±5.30	36.89±5.24	40.39±4.76	0.023
CEA	Median (Range)	1.5 (0.2-226.2)	1.7 (0.2-57.8)	1.05 (0.2-4.4)	0.083
CA 19-9	Median (Range)	13.4 (1.2-879)	12.8 (1.2-879)	14.8 (5.6-59.3)	0.417
CA 72-4	Median (Range)	2.5 (0.1-440)	2.85 (0.1-440)	2.0 (0.1-145.3)	0.069
Type	Intestinal	46 (38.3)	30 (36.2)	16 (43.2)	0.586
	Mixed	7 (5.8)	6 (7.2)	1 (2.7)	
	Diffuse	67 (55.9)	47 (56.6)	20 (54.1)	
NACT	Yes	14 (11.7)	9 (10.8)	5 (13.5)	0.760
	No	106 (88.3)	74 (89.2)	32 (86.5)	
Surgery	Radical	110 (91.7)	73 (64.8)	37 (100)	0.030
	Palliative	10 (8.3)	10 (12.0)	0 (0)	
Outcome	Dead	56 (46.7)	46 (88.0)	10 (27.0)	0.0005
	Survived	64 (53.3)	37 (44.6)	27 (73.0)	

LN: Lymph nodes; (%)*: expressed as percentage of the column total, if applicable; *p*-Value: probability value; SD: standard deviation; CRP: C-reactive protein; Neu/Ly: neutrophil-to-lymphocyte (ratio); NACT: neoadjuvant therapy.

Table III. *Multivariable logistic model for lymph-node involvement in gastric cancer patients.*

Variable	B coefficient	Standard error	*p*-Value	OR	95%CI
(Intercept)	–1.984	1.731	0.252	n.a.	
Age	–0.012	0.021	0.580	0.988	0.948 to 1.030
Male gender	1.427	0.503	0.005	4.168	1.554 to 11.18
Fibrinogen	0.649	0.307	0.034	1.914	1.049 to 3.494
Diffuse or mixed type	0.902	0.522	0.084	2.465	0.886 to 6.858

Logit model: Deviance (likelihood ratio) chi-square=15.54; *p*-Value=0.0037. Diagnostic performance at probability cut-off at max(sens+spec) of 0.66: PPV=84%; NPV=50% and AUC=72.8%. *p*-Value: probability value; OR: odds ratio; CI: confidence interval; n.a.: not applicable; PPV: positive predictive value; NPV: negative predictive value; AUC: area under ROC curve.

For patients without LN involvement the 5-year survival was 72.9% with 95%CI=86.1-51.4, and for patients with present LN involvement levels it was 35.1% with 95%CI=47.2-23.2. For patients with unproven but conceivably present involvement the 5-year survival could not be estimated. Here we present the 3-year survival of 6.3% (95%CI=24.1-0.4). These differences were significant ($p<0.0001$, Figure 1, lower left). The five-year survival varied with stage of disease from 76.1% (95%CI=87.7-56.7) for stage I-II to 43.4% (95%CI=60.1-25.4) for stage III, and to 5.2% (95%CI=18.3-0.6) for stage IV. These differences were significant ($p<0.0001$, Figure 1, lower right).

Discussion

Despite adequate surgery with radical lymphadenectomy the prognosis of GC is still poor. The five-year survival of patients with early GC is about 75%, but at an advanced stage with extensive LN involvement it is less than 30% (41). In order to improve long-term survival new more effective treatment modalities are tested. An important aim is to personalize (tailor) treatment according to the characteristics of the individual patient (42, 43). Endoscopic resection is appropriate for very small tumors. For stage IB–III gastric cancer, radical gastrectomy is indicated and perioperative therapy is

recommended for these patients. Medically fit patients should undergo D2 resections in high-volume surgical centers (44). Since the end of the 1980s, more patients with locally advanced tumors were subjected to a preoperative, perioperative or postoperative treatment in order to improve the prognosis after resection (41). Therefore, the contribution of perioperative chemotherapy is tested in order to improve survival. It was documented that perioperative chemotherapy leads to downsizing of the primary tumor, significantly improves progression-free survival, and significantly improves overall survival and should be considered as a treatment of choice for patients with potentially curable GC.

Specification of LN involvement prior to surgery is limited, as the detection rates of the imaging tests may vary. The logistic model constructed from risk factors from multivariate analysis in this study, may be an effective diagnostic approach. Therefore, using clinical data of GC patients, we investigated risk prediction models considering various combinations of preoperatively known characteristics, in order to select a proper set of explanatory variables that are either known to affect the risk of LN involvement or might be confounders. Specifically, we have investigated the relationship between LN metastasis and levels of FBG, ALB, CRP, tumor markers CEA, CA 19-9, CA 72-4 and ratio NLR. We were focused on preoperative levels of FBG and ALB that had been significantly associated with nodal status in patients with GC in bivariable analysis. The best model was composed of four variables known before surgery which proved to be most efficient in predicting the LN involvement: age, sex, and histology of tumor and FBG.

In 1975 Brajerski reported that increased FBG level was observed in 67% of GC patients (45). The tumor itself may be a source of FBG and it is one of the factors of the tumor growth and metastasis (46). The adverse effect of hyperfibrinogenemia on the long-term survival as well as the increased risk of metastases in patients with gastrointestinal tract malignancies was confirmed by further studies (47-49). Several studies have confirmed this link for GC as well (33, 50, 51). In 2006 Yamashita reported that hyperfibrinogenemia is associated with lymphatic and hematogenous metastasis and worse clinical outcome (52). His results are confirmed by other studies demonstrating the utility of FBG in the prediction of node involvement in GC patients (53, 54).

In our study, 120 patients had histologically examined LNs. Fifty-four of them had FBG level greater than 3.5 g/l; histologically confirmed LN metastases were present in 43 cases (79.6%). Changes in FBG and ALB levels were significantly associated with the presence of LN metastases. Decrease in serum ALB concentration and elevation of FBG level represents an increased risk of LN involvement (p=0.023, resp. 0.008). Furthermore, elevated FBG was associated with worse prognosis reflected in reduced long-term survival (p=0.034).

Conventional tumor markers CEA, CA 19-9, CA 72-4 are widely used for monitoring response to therapy and detection of recurrence (10), but their sensitivity in detection of LN metastases is limited. In our study, patients with LN involvement had increased levels of CEA and CA 72-4, but these markers were not significant predictors of lymphoid metastases *per se* (p=0.083, resp. 0.069). However, they still can improve overall model performance of prediction models for measures of binary and survival outcomes. Other tested markers (CA 19-9, NLR, CRP) did not contribute significantly to the prediction of LN involvement. Given that presence of LN metastases influences therapeutic decision, routine clinical laboratory testing of FBG and ALB levels may bring additional information for determining if perioperative chemotherapy should be given. In addition, altered levels of FBG and ALB indicate the necessity of thorough lymphadenectomy. Even extensive LN dissections have promising results when performed by experienced surgeons in high-volume centers (55, 56). To assess whether perioperative chemotherapy and a precise lymph node dissection might play some role in prolonging survival after surgery requires a longitudinal clinical study in a large series of GC patients. Then the risk of LN involvement as predicted by logistic regression can be used in a Cox proportional hazard regression to examine whether these approaches will prolong survival.

Conclusion

We have developed a model for prediction of LN involvement in order to improve preoperative cancer staging. Based on our findings we conclude that alteration in fibrinogen and albumin levels can serve as indicators of node involvement in patients with GC. Timely and more accurate information about the staging can help clinicians to optimize patients' treatments. The ultimate goal of preoperative management of a GC patient is to improve overall outcome. Future validation study using prospective cohort is highly recommended to strengthen our conclusions.

Conflicts of Interest

Július Palaj, Štefan Kečkéš, Vítězslav Marek, Daniel Dyttert, Iveta Waczulíková, Štefan Durdík have no conflicts of interest or financial ties to disclose.

References

1 Ferlay J, Shin HR BF *et al*: GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC Cancer- Base No. 10. Int Agency Res Cancer, Lyon, France, 2010.

2 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer *136*: E359-E386, 2015.

3 Fock KM: Review article: the epidemiology and prevention of gastric cancer. Aliment Pharmacol Ther *40*: 250-260, 2014.

4 Van Cutsem E, Dicato M, Geva R, Arber N, Bang Y, Benson A, Cervantes A, Diaz-Rubio E, Ducreux M, Glynne-Jones R, Grothey A, Haller D, Haustermans K, Kerr D, Nordlinger B, Marshall J, Minsky BD, Kang YK, Labianca R, Lordick F, Ohtsu A, Pavlidis N, Roth A, Rougier P, Schmoll HJ, Sobrero A, Tabernero J, Van de Velde C and Zalcberg J: The diagnosis and management of gastric cancer: expert discussion and recommendations from the 12th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2010. Ann Oncol *22 5*: v1-9, 2011.

5 Bouvier A-M, Sant M, Verdecchia A, Forman D, Damhuis R, Willem Coebergh J, Crocetti E, Crosignani P, Gafa L, Launoy G, Martinez-Garcia C, Plesko I, Pompe-Kirn V, Rachtan J, Velten M, Vercelli M, Zwierko M, Esteve J and Faivre J: What reasons lie behind long-term survival differences for gastric cancer within Europe? Eur J Cancer *46*: 1086-1092, 2010.

6 Yokota T, Ishiyama S, Saito T, Teshima S, Narushima Y, Murata K, Iwamoto K, Yashima R, Yamauchi H and Kikuchi S: Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. Scand J Gastroenterol *39*: 380-384, 2004.

7 Shiraishi N, Sato K, Yasuda K, Inomata M and Kitano S: Multivariate prognostic study on large gastric cancer. J Surg Oncol *96*: 14-18, 2007.

8 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ and MAGIC Trial Participants: Perioperative Chemotherapy *versus* Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med *355*: 11-20, 2006.

9 Ychou M, Boige V, Pignon J-P, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre J-M, Saint-Aubert B, Genève J, Lasser P and Rougier P: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol *29*: 1715-1721, 2011.

10 Shimada H, Noie T, Ohashi M, Oba K and Takahashi Y: Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. Gastric Cancer *17*: 26-33, 2014.

11 Marrelli D, Roviello F, De Stefano A, Farnetani M, Garosi L, Messano A and Pinto E: Prognostic significance of CEA, CA 19-9 and CA 72-4 preoperative serum levels in gastric carcinoma. Oncology *57*: 55-62, 1999.

12 Sun Z and Zhang N: Clinical evaluation of CEA, CA19-9, CA72-4 and CA125 in gastric cancer patients with neoadjuvant chemotherapy. World J Surg Oncol *12*: 397, 2014.

13 Gaspar MJ, Arribas I, Coca MC and Díez-Alonso M: Prognostic value of carcinoembryonic antigen, CA 19-9 and CA 72-4 in gastric carcinoma. Tumour Biol *22*: 318-322, 2001.

14 Tocchi A, Costa G, Lepre L, Liotta G, Mazzoni G, Cianetti A and Vannini P: The role of serum and gastric juice levels of carcinoembryonic antigen, CA19.9 and CA72.4 in patients with gastric cancer. J Cancer Res Clin Oncol *124*: 450-455, 1998.

15 Ucar E, Semerci E, Ustun H, Yetim T, Huzmeli C and Gullu M: Prognostic value of preoperative CEA, CA 19-9, CA 72-4, and AFP levels in gastric cancer. Adv Ther *25*: 1075-1084, 2008.

16 Byrne DJ, Browning MC and Cuschieri A: CA72-4: a new tumour marker for gastric cancer. Br J Surg *77*: 1010-1013, 1990.

17 Spila A, Roselli M, Cosimelli M, Ferroni P, Cavaliere F, Arcuri R, Tedesco M, Carlini S, D'Alessandro R, Perri P, Casciani CU, Greiner JW, Schlom J and Guadagni F: Clinical utility of CA 72-4 serum marker in the staging and immediate post-surgical management of gastric cancer patients. Anticancer Res *16*: 2241-2247, 1996.

18 Carpelan-Holmström M, Louhimo J, Stenman UH, Alfthan H and Haglund C: CEA, CA 19-9 and CA 72-4 improve the diagnostic accuracy in gastrointestinal cancers. Anticancer Res *22*: 2311-2316, 2002.

19 Hamazoe R, Maeta M, Matsui T, Shibata S, Shiota S and Kaibara N: CA72-4 compared with carcinoembryonic antigen as a tumour marker for gastric cancer. Eur J Cancer *28A*: 1351-1354, 1992.

20 Hanahan D and Weinberg RA: Hallmarks of Cancer: The Next Generation. Cell *144*: 646-674, 2011.

21 Colotta F, Allavena P, Sica A, Garlanda C and Mantovani A: Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis *30*: 1073-1081, 2009.

22 Ide S, Toiyama Y, Okugawa Y, Oki S, Yasuda H, Fujikawa H, Yoshiyama S, Hiro J, Kobayashi M, Ohi M, Araki T and Kusunoki M: Clinical significance of C-reactive protein-to- albumin ratio with rectal cancer patient undergoing chemoradiotherapy followed by surgery. Anticancer Res *37*: 5797-5804, 2017.

23 Hirahara N, Matsubara T, Kawahara D, Nakada S, Ishibashi S and Tajima Y: Prognostic significance of preoperative inflammatory response biomarkers in patients undergoing curative thoracoscopic esophagectomy for esophageal squamous cell carcinoma. Eur J Surg Oncol *43*: 493-501, 2017.

24 Jagadesham VP, Lagarde SM, Immanuel A and Griffin SM: Systemic inflammatory markers and outcome in patients with locally advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. Br J Surg *104*: 401-407, 2017.

25 Yamashita K, Ushiku H, Katada N, Hosoda K, Moriya H, Mieno H, Kikuchi S, Hoshi K and Watanabe M: Reduced preoperative serum albumin and absence of peritoneal dissemination may be predictive factors for long-term survival with advanced gastric cancer with positive cytology test. Eur J Surg Oncol *41*: 1324-1332, 2015.

26 Chen J, Zhou Y, Xu Y, Zhu H-Y and Shi YQ: Low pretreatment serum globulin may predict favorable prognosis for gastric cancer patients. Tumor Biol *37*: 3905-3911, 2016.

27 Isik, A1. Isik A, Okan I, Firat D, Yilmaz B, Akcakaya A and Sahin M: A new prognostic strategy for gastric carcinoma: albumin level and metastatic lymph node ratio. Minerva Chir *69*: 147-153, 2014.

28 Chang CC, Sun CF, Pai HJ, Wang WK, Hsieh CC, Kuo LM and Wang CS: Preoperative serum C-reactive protein and gastric cancer; clinical-pathological correlation and prognostic significance. Chang Gung Med J *33*: 301-312, 2010.

29 Grenader T, Waddell T, Peckitt C, Oates J, Starling N, Cunningham D and Bridgewater J: Prognostic value of neutrophil-to-lymphocyte ratio in advanced oesophago-gastric cancer: exploratory analysis of the REAL-2 trial. Ann Oncol *27*: 687-692, 2016.

30 Hu ZD, Huang YL, Qin BD, Tang QQ, Yang M, Ma N, Fu HT, Wei TT and Zhong RQ: Prognostic value of neutrophil to lymphocyte ratio for gastric cancer. Ann Transl Med *3*: 50, 2015.

31 Zhang X, Zhang W and Feng L: Prognostic significance of neutrophil lymphocyte ratio in patients with gastric cancer: a meta-analysis. PLoS One *9*: e111906, 2014.

32 Shimada H, Takiguchi N, Kainuma O, Soda H, Ikeda A, Cho A, Miyazaki A, Gunji H, Yamamoto H and Nagata M: High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer *13*: 170-176, 2010.

33 Lee SE, Lee JH, Ryu KW, Nam BH, Cho SJ, Lee JY, Kim CG, Choi IJ, Kook MC, Park SR and Kim YW: Preoperative plasma fibrinogen level is a useful predictor of adjacent organ involvement in patients with advanced gastric cancer. J Gastric Cancer *12*: 81-87, 2012.

34 Jiang HG, Li J, Shi SB, Chen P, Ge LP, Jiang Q and Tang XP: Value of fibrinogen and D-dimer in predicting recurrence and metastasis after radical surgery for non-small cell lung cancer. Med Oncol *31*: 22, 2014.

35 Kim KH, Park TY, Lee JY, Lee SM, Yim JJ, Yoo CG, Kim YW, Han SK and Yang SC: Prognostic significance of initial platelet counts and fibrinogen level in advanced non-small cell lung cancer. J Korean Med Sci *29*: 507-511, 2014.

36 Zhu JF, Cai L, Zhang XW, Wen YS, Su XD, Rong TH and Zhang LJ: High plasma fibrinogen concentration and platelet count unfavorably impact survival in non-small cell lung cancer patients with brain metastases. Chin J Cancer *33*: 96-104, 2014.

37 Sheng L, Luo M, Sun X, Lin N, Mao W and Su D: Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. Int J cancer *133*: 2720-2725, 2013.

38 Matsuda S, Takeuchi H, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, Wada N, Saikawa Y, Omori T and Kitagawa Y: Cumulative prognostic scores based on plasma fibrinogen and serum albumin levels in esophageal cancer patients treated with transthoracic esophagectomy: Comparison with the Glasgow Prognostic Score. Ann Surg Oncol *22*: 302-310, 2015.

39 Sobin LH and Compton CC: TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer *116*: 5336-5339, 2010.

40 Association JGC: Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer *14*: 101-112, 2011.

41 Schirren R, Reim D and Novotny AR: Adjuvant and/or neoadjuvant therapy for gastric cancer? A perspective review. Ther Adv Med Oncol *7*: 39-48, 2015.

42 Smyth EC and Cunningham D: Targeted therapy for gastric cancer. Curr Treat Options Oncol *13*: 377-389, 2012.

43 Lim SM, Lim JY and Cho JY: Targeted therapy in gastric cancer: personalizing cancer treatment based on patient genome. World J Gastroenterol *20*: 2042-2050, 2014.

44 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A and Arnold D: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *27*: v38-v49, 2016.

45 Brajerski W, Sikorska K, Bisztyga A and Ilenda M: Blood fibrinogen level in peptic ulcer and gastric carcinoma. Pol Med Sci Hist Bull *15*: 557-560, 1975.

46 Kołodziejczyk J and Ponczek MB: The role of fibrinogen, fibrin and fibrin(ogen) degradation products (FDPs) in tumor progression. Contemp Oncol (Poznan, Poland) *17*: 113-119, 2013.

47 Shu YJ, Weng H, Bao RF, Wu XS, Ding Q, Cao Y, Wang XA, Zhang F, Xiang SS, Li HF, Li ML, Mu JS, Wu WG and Liu YB: Clinical and prognostic significance of preoperative plasma hyperfibrinogenemia in gallbladder cancer patients following surgical resection: a retrospective and *in vitro* study. BMC Cancer *14*: 566, 2014.

48 Wang J, Liu H, Shao N, Tan B, Song Q, Jia Y and Cheng Y: The clinical significance of preoperative plasma fibrinogen level and platelet count in resectable esophageal squamous cell carcinoma. World J Surg Oncol *13*: 157, 2015.

49 Wakatsuki K, Matsumoto S, Migita K, Ito M, Kunishige T, Nakade H, Nakatani M, Kitano M and Sho M: Preoperative plasma fibrinogen is associated with lymph node metastasis and predicts prognosis in resectable esophageal cancer. World J Surg *41*: 2068-2077, 2017.

50 Yu X, Hu F, Yao Q, Li C, Zhang H and Xue Y: Serum fibrinogen levels are positively correlated with advanced tumor stage and poor survival in patients with gastric cancer undergoing gastrectomy: a large cohort retrospective study. BMC Cancer *16*: 480, 2016.

51 Suzuki T, Shimada H, Nanami T, Oshima Y, Yajima S, Ito M, Washizawa N and Kaneko H: Hyperfibrinogenemia is associated with inflammatory mediators and poor prognosis in patients with gastric cancer. Surg Today *46*: 1394-1401, 2016.

52 Yamashita H, Kitayama J, Kanno N, Yatomi Y and Nagawa H: Hyperfibrinogenemia is associated with lymphatic as well as hematogenous metastasis and worse clinical outcome in T2 gastric cancer. BMC Cancer *6*: 147, 2006.

53 Yu W, Wang Y and Shen B: An elevated preoperative plasma fibrinogen level is associated with poor overall survival in Chinese gastric cancer patients. Cancer Epidemiol *42*: 39-45, 2016.

54 Lee JH, Ryu KW, Kim S and Bae JM: Preoperative plasma fibrinogen levels in gastric cancer patients correlate with extent of tumor. Hepatogastroenterology *51*: 1860-1863, 2004.

55 Degiuli M, Sasako M, Ponti A and Italian Gastric Cancer Study Group: Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 *versus* D2 resection for gastric cancer. Br J Surg *97*: 643-649, 2010.

56 Enzinger PC, Benedetti JK, Meyerhardt JA, McCoy S, Hundahl SA, Macdonald JS and Fuchs CS: Impact of hospital volume on recurrence and survival after surgery for gastric cancer. Ann Surg *245*: 426-434, 2007.

Received November 17, 2017
Revised December 13, 2017
Accepted December 14, 2017