Inflammatory and nutritional status is a predictor of long-term outcome in patients undergoing surgery for gastric cancer.

Validation of the Naples prognostic score

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Inflammatory and nutritional status is a predictor of long-term outcome in patients undergoing surgery for gastric cancer. Validation of the Naples prognostic score

PURPOSE: *Oncological outcome depends not only on tumor behaviour but also on nutritional and immune-inflammatory host status. Data in gastric cancer are limited. The main aim of this study was to prospectively assess Naples prognostic score (NPS) in gastric cancer patients. NPS was also compared with prognostic nutritional index (PNI), controlling nutritional status (CONUT) score and systemic inflammation score (SIS).*
METHODS: *Overall survival (OS) and complication rates of 415 patients undergoing gastric cancer surgery from January 2000 to December 2015 were calculated. Disease-free survival (DFS) rates were assessed in 307 radically resected patients. MaxStat analysis was used to identify the best cut-off values. NPS scores were divided into 3 groups (NPS 0-3). The receiver-operating-characteristic (ROC) curve for censored survival data was used to compare the prognostic performance of scoring systems.*
RESULTS: *NPS positively correlated with current scoring systems ($p<0.001$) and advanced tumor stages ($p<0.001$). Patients with elevated NPS scores experienced more postoperative complications (all patients: $p=0.003$; radically resected patients: $p=0.010$). NPS1 and NPS2 patients had a higher hazard ratio (HR) than NPS0 patients for OS (NPS1 HR 2.04, NPS2 HR 4.27; $p<0.001$) and DFS (NPS1 HR 1.70, NPS2 HR 4.98; $p<0.001$). Among the different scoring systems, only NPS was selected as an independent significant predictor for OS ($p=0.024$) and DFS ($p=0.009$). NPS was assigned the best prognostic performance by ROC analysis, equalling TNM staging system, and correctly identified high-risk patients.*
CONCLUSIONS: *NPS is an easy to calculate prognostic score strongly associated with outcome in patients undergoing gastric cancer surgery.*

KEY WORDS: Gastric cancers, Immune-nutritional and inflammatory host status, Naples prognostic score

Introduction

Current treatment and prognosis of gastric cancer are mainly based on pathological staging; however, a high recurrence rate renders long-term results still disappointing [1-3]. Wider implementation of different combinations of neo- and adjuvant therapies are expected to achieve better outcomes, and identification of prognostic indicators able to detect high risk patients is very desirable [4]. There is growing evidence that not only tumor status but also host characteristics may influence the course of several human malignancies, including gastric cancer [5-8]. The neutrophil-to-lymphocyte ratio (NLR) and the lymphocyte-to-monocyte ratio (LMR) have been shown to be reliable surrogate indicators of the host

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inflammatory and immunological status [7,9-12]. In addition, preoperative serum levels of albumin and cholesterol have been demonstrated to correctly reflect the nutritional status [13-16]. These biological markers, alone or in combination, have been proposed to predict outcome in many human tumors, particularly colorectal and liver cancers [17,18]. However, the lack of accurate analyses of score prognostic performances has limited their diffusion [19]. In addition, experiences in gastric cancers are conflicting and limited to a single marker [20,21]. Only a few studies have investigated different associations of these markers, namely NLR and LMR [22], PNI (Prognostic Nutritional Index) [13-15,23], and CONUT (Controlling Nutritional Status) [13,16], without clarifying their clinical utility [24]. Moreover, the SIS (Systemic Inflammation Score), which has recently sparked some interest in renal and colon cancer, has never been investigated in gastric cancer patients [19,25].

Materials and Methods

We have recently demonstrated that a new prognostic score, the so-called Naples prognostic score (NPS), based on the association of markers reflecting on the one hand the inflammatory and immunological status (NLR and LMR) and the nutritional status (albumin and cholesterol levels) on the other, was an independent indicator of outcome in colorectal cancer patients undergoing surgery. NPS was also shown to display the best prognostic performance, nearly matching the TNM staging system, when compared to previously developed prognostic systems [26]. The aim of this study was therefore to investigate the prognostic role of NPS and its correlations with other scoring systems in a large series of gastric cancer patients undergoing surgery.

Patient Cohort

Clinical characteristics and pathological findings of patients undergoing surgery for proven gastric adenocarcinoma, from January 2000 to December 2015, were retrieved from a prospectively maintained comprehensive database. Blood tests were routinely performed in the week before surgery. In patients subjected to preoperative chemotherapy, these data were collected not earlier than 5 weeks after the end of therapy, since modifications in circulating blood cell counts have been shown to normalize after this time [27]. After discharge, adjuvant chemotherapy was offered to radically resected pT3 and/or node positive patients; metastatic and non-radically treated patients underwent chemotherapy [28]. All patients signed written consent to use their data, and were followed up until death or June 30, 2017, whichever came first. Institutional Review Board (IRB) approval was obtained from the Ethical Committee (protocol number 196/2017, Naples 06.05.2017), and the study was registered at ClinicalTrials.gov with *PRS* number ID: NCT03272646.

Postoperative complications were defined as grade II or higher of the Clavien-Dindo classification [29]. PNI was initially calculated as a continuous variable: (10 x albumin value (g/dL)) + (0.005 x TLC, i.e., total lymphocyte count, in the peripheral blood), with lower values indicating impairment of the host status [30]. CONUT, including albumin level ≥ 3.5 g/dL, total cholesterol > 180 mg/dL, and TLC ≥ 1600/μL, was calculated by assigning each patient a score ranging from 0 to 12, with higher values indicating alterations of the nutritional status [31,32]. SIS was calculated as previously described (patients with serum albumin level ≥ 4 g/dL and LMR level ≥ 4.44 were assigned a score of 0; a score of 1 was allocated to patients with hypoalbuminemia or a low LMR; patients with hypoalbuminemia and low LMR were attributed a score of 2) [19,25,26]. According to our previous experience in colorectal cancers, NPS was calculated based on the following 4 parameters: serum albumin (normal: ≥4g/dl), total cholesterol (normal: >180 mg/dl), NLR (normal: ≤2.96), and LMR (normal: >4.44) [26]. Each parameter was assigned a score (normal value = 0, altered value = 1), and patients were initially assigned a score of 0 to 4. Afterwards, patients were divided into three groups: patients with score = 0 were assigned to group 0 (normal values for all 4 parameters); patients with score 1 or 2 were assigned to group 1 (one or two altered values); and patients with score 3 or 4 were assigned to group 2 (three or four altered values).

Analysis of postoperative complications and overall survival (OS) was performed for all patients (survival analysis data set). Recurrence and disease-free survival (DFS) rates were computed for patients undergoing potentially curative surgery (recurrence analysis data set).

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQR). The chi-square test was used to analyze correlations between NPS and other prognostic factors or other score systems. Continuous variables were dichotomized by using median values (age and tumor size), normal values (CEA, serum albumin levels, and plasma total cholesterol), or in accordance with previous investigations (TLC) [26,33]. The R package MaxStat was used to dichotomize NLR, LMR, PNI, and CONUT in the current series [34]. The Kaplan-Meier method and long-rank test were used to compare survival curves. Univariate and multivariate analyses were performed by using the Cox proportional hazards regression model; specifically, prognostic variables showing $p < 0.1$ on univariate analysis were included in the multivariate analysis. The prognostic performance of the dif-

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ferent score systems was assessed by analyzing homogeneity with the likelihood ratio chi-square test as well as monotonicity with the linear trend chi-square test [35]. The improvement in risk prediction of each prognostic system was assessed by the time-dependent receiver operating characteristic (ROC) curve for censored survival data using the area-under-curve (AUC), which estimates the probability that, at a certain time point, a patient with an event is classified in a higher staging category than a patient who does not present the event at that time [26,36]. Higher AUC values were associated with a better predictive ability. All analyses were two-sided; $p < 0.05$ was considered to be statistically significant. Statistical analyses were carried out using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and the statistical package R (version 3.3.29).

Results

Out of 477 consecutive patients, 62 patients were excluded from the study because of lack of data (n=25), or because of concomitant conditions potentially able to affect white blood cell counts (n=37). The survival data set included a total of 415 patients; 307 patients undergoing a potentially curative treatment constituted the recurrence data set (Fig. 1). In both groups, NPS significantly correlated with other score systems ($p < 0.001$). Moreover, NPS worsened with older age, worse performance status, non-radicality, advanced Bormann's types, and advanced TNM stage (Supplemental Table I). Postoperative complication rates increased with worsening NPS scores. In patients with no or only slight alterations of nutritional and inflammatory status, rates were low (12.5% and 16.8%, respectively). On the contrary, patients with three or four altered NPS values had a complication rate of 28.7% ($p = 0.0029$).

Survival And Recurrence Analyses

Median follow-up time was 22.7 months (IQR: 9.1-55.9 months). In this time frame, 237 patients (57.1%) died, 12 of them perioperatively (2.9%). The 1- to 5-year OS rates were 70.5, 55.2, 44.7, 40.9, and 38.0%, respectively, and were significantly related to several prognostic factors, including hypoalbuminemia, hypocholesterolemia, elevated NLR, and decreased LMR values ($p < 0.001$). PNI, CONUT, SIS, and NPS were also shown to be significantly ($p < 0.001$) related to OS on univariate analysis (Table I). Five-year OS rates significantly worsened as NPS score increased from 0 to 4. Patients with NPS scores 1 and 2 displayed a quite similar outcome, as did patients with NPS scores 3 and 4, suggesting that categorizing patients into only three groups did not affect NPS significance (Supplemental Fig. 1). Interestingly, 5-year OS rates in NPS groups 0, 1, and 2 were 65.9, 40.6, and 13.9%, respectively ($p < 0.001$). The estimated relative risk of death of NPS0 patients was 51% and 75% lower than that of NPS1 and NPS2 patients, respectively; NPS1 patients had a 52% lower relative risk of death than NPS2 patients (Fig. 2A). On multivariate analysis, when individually considered, all biomarkers but hypoalbuminemia were not shown to correlate with long-term outcome; current scoring systems were not demonstrated to be independent prognostic factors for survival (Table I). On the contrary, NPS significantly correlated with survival and was shown to be an independent prognostic factor ($p = 0.024$).

In the recurrence analysis data set, the median follow-up time for DFS was 21.0 months (IQR: 7.94-54.9 months). Within this time frame, 97 patients (31.6%) experienced tumor relapse. Recurrence rates were 23, 27, and 46% in NPS groups 0, 1, and 2, respectively ($p = 0.0017$). The 1- to 5-year DFS rates were 77.8, 66.1, 57.3, 55.4, and 52.4%, respectively, and were related to the same factors involved in OS analysis, including the individual markers (Table II). Similarly, all four prognostic scoring systems were shown to be significantly related to DFS rates, with NPS showing the greatest differences (Fig. 2B). On multivariate analysis, when individually analyzed, any considered biomarker failed to show any significance. Among the four scoring systems analyzed, only NPS was shown to be significantly related to DFS rate (Table II).

Prognostic Performance

Compared to the OS rate, the four different scoring systems showed different homogeneity and monotonicity (Table III). Particularly, NPS was shown to best allocate patients with the same survival rate. Time-dependent ROC curves with estimated AUCs calculated at different time points for each scoring system, including, for comparison, the TNM staging system, clearly showed NPS to be continuously superior to other scoring systems at each time point; besides, at five years, NPS nearly equaled the prognostic power of TNM system (Fig. 3A). Also, in the recurrence data set, NPS was shown to have the best prognostic performance and AUC values. Interestingly, NPS had a uniformly better curve than other scoring systems, even superior to TNM curve, thus showing the best ability to predict tumor recurrence (Fig. 3B).

Discussion

This study shows that NPS is an independent predictor of outcome in patients undergoing surgery for gastric cancer. Patients with high NPS values had a greater risk of severe postoperative complications as well as significantly lower OS and DFS rates. When compared to pre-

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Table I - *Clinico-pathological characteristics and univariate and multivariate analyses of overall survival rates in 415 patients with gastric cancer who underwent surgery*

			Univariate Analyses			Multivariate Analyses		
Factor	**Nr. Pts**	**% 5-years OS**	**HR**	**95%CI HR a**	**P value**	**HR**	**95%CI HR a**	**P value**
Age [b]								
≤ 65 years	219	40.7	1	Referent	0.033	1	Referent	0.086
> 65 years	196	35.0	1.32	1.02-1.70		1.01	0.99-1.02	
Gender								
Male	243	43.2	1	Referent	0.037	1	Referent	0.486
Female	172	30.6	1.31	1.01-1.69		1.12	0.81-1.55	
CEA								
≤ 3.5 ng/mL	306	39.9	1	Referent	0.027	1	Referent	0.105
> 3.5 ng/mL	109	32.4	1.36	1.03-1.80		1.34	0.94-1.92	
CA19-9								
≤ 37 U/mL	283	45.0	1	Referent	<0.001	1	Referent	0.412
> 37 U/mL	132	22.7	1.96	1.51-2.54		1.15	0.81-1.63	
PS								
0	135	56.1	1	Referent	<0.001	1	Referent	0.780
1/2	280	28.9	2.27	1.67-3.07		1.06	0.68-1.64	
Tumor Site								
Distal	166	42.8	1	Referent	0.034	1	Referent	0.253
Middle Third	131	40.7	1.09	0.79-1.49		1.37	0.93-2.04	
Upper Third	118	26.9	1.48	1.08-2.01		1.23	0.85-1.78	
PreOP Ch.								
Yes	42	48.9	1	Referent	0.798	//	//	//
No	373	37.3	1.07	0.63-1.81				
Radicality								
Yes	307	50.8	1	Referent	<0.001	1	Referent	<0.001
No	108	2.1	5.28	4.00-6.98		2.05	1.37-3.06	
Macroscopic Type [c]								
Mass	57	63.3	1	Referent		1	Referent	
Ulcerative	138	53.8	1.49	0.88-2.53	<0.001	1.44	0.76-2.74	0.004
Ulcerative infiltrative	133	31.0	2.20	1.32-3.67		1.92	1.01-3.63	
Diffuse infiltrative	87	6.4	5.82	3.46-9.78		3.42	1.62-7.22	
Histological Type								
Differentiated	213	47.2	1	Referent	<0.001	1	Referent	0.023
Undifferentiated	202	27.2	1.73	1.33-2.23		1.68	1.07-2.63	
Lauren's classification								
Intestinal	188	51.1	1	Referent	<0.001	1	Referent	0.019
Diffuse	227	26.6	2.11	1.62-2.76		1.81	1.10-2.99	
PO Complic.								
No	335	40.7	1	Referent	<0.001	1	Referent	<0.001
Yes	80	26.4	1.72	1.28-2.33		2.46	1.62-3.72	
PO Ch.								
No	131	48.4	1	Referent	0.075	1	Referent	0.040
Yes	284	33.5	1.29	0.97-1.73		1.52	1.01-2.28	
TNM stage [d]								
IA	72	88.1	1	Referent		1	Referent	
IB	42	55.3	3.23	1.46-7.12		2.66	1.13-6.27	
IIA	56	44.0	4.84	2.34-9.98		5.08	2.25-11.44	
IIB	85	31.9	6.39	3.25-12.55	<0.001	4.68	2.16-10.13	<0.001
IIIA	70	16.0	11.76	5.94-23.30		12.15	5.57-26.46	
IIIB	27	0.0	13.67	6.49-28.78		12.91	5.59-29.87	
IIIC	18	23.9	11.32	4.69-27.30		2.81	0.92-8.60	
IV	45	0.0	49.38	28.82-92.38		18.76	7.48-47.07	
Albumin								
≥ 4 g/dL	264	45.9	1	Referent	<0.001	1	Referent	0.020
< 4 g/dL	151	24.7	1.71	1.32-2.21		1.65	1.08-2.53	
Cholesterol								
> 180 mg/dL	221	49.1	1	Referent	<0.001	1	Referent	0.655
≤ 180 mg/dL	194	25.3	2.05	1.58-2.65		1.10	0.72-1.67	

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Table I - *Clinico-pathological characteristics and univariate and multivariate analyses of overall survival rates in 415 patients with gastric cancer who underwent surgery*

			Univariate Analyses			Multivariate Analyses		
Factor	**Nr. Pts**	**% 5-years OS**	**HR**	**95%CI HR a**	**P value**	**HR**	**95%CI HR a**	**P value**
Lymphocytes								
> 1600 mm^3	215	47.3	1	Referent	<0.001	1	Referent	0.094
≤ 1600 mm^3	200	27.0	1.61	1.25-2.09		1.46	0.93-2.30	
NLR [e]								
≤ 3.22	289	48.4	1	Referent	<0.001	1	Referent	0.898
> 3.22	126	13.9	2.43	1.87-3.15		1.03	0.62-1.70	
LMR [e]								
> 3.48	252	49.7	1	Referent	<0.001	1	Referent	0.947
≤ 3.48	163	20.4	2.17	1.68-2.80		1.02	0.47-2.19	
PNI [e]								
> 49	253	50.0	1	Referent	<0.001	1	Referent	0.266
≤ 49	162	20.3	2.21	1.71-2.86		1.42	0.76-2.68	
CONUT [e]								
≤ 1	251	52.2	1	Referent	<0.001	1	Referent	0.306
> 1	164	13.8	2.66	2.05-3.45		1.28	0.79-2.05	
SIS								
0	146	51.8	1	Referent	<0.001	1	Referent	0.375
1	152	39.4	1.45	1.05-2.00		1.29	0.40-4.18	
2	117	18.9	2.35	1.69-3.26		0.86	0.42-1.75	
NPS score								
0	80	65.9	1	Referent				
1	116	43.0	1.86	1.16-2.97				
2	104	37.5	2.26	1.42-3.59	<0.001	//	//	//
3	49	21.9	3.78	2.26-6.31				
4	66	8.9	4.67	2.90-7.53				
NPS group [f]								
0	80	65.9	1	Referent	<0.001	1	Referent	0.024
1	220	40.6	2.04	1.33-3.14		1.80	0.95-3.41	
2	115	13.9	4.27	2.73-6.66		4.59	1.52-13.81	

HR= hazard ratio; CEA= carcinoembryonic antigen (normal level 3.5 ng/mL); CA19-9= carbohydrate antigen 19-9 (normal level 37 U/mL); PS= performance status according to ECOG scale; PreOP Ch.= preoperative chemotherapy; PO Complic.= postoperative complications defined as grade II or higher of the Clavien-Dindo classification (reference n. 29); PO Ch=postoperative chemotherapy; NLR= neutrophil to lymphocyte ratio; LMR= lymphocyte to monocyte ratio; PNI= prognostic nutritional index, calculated as follows: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count in the peripheral blood; CONUT= controlling nutritional status, a scoring system calculated by summing the value of serum albumin, total cholesterol, and total lymphocyte count in the peripheral blood; SIS= system inflammation score based on serum albumin and lymphocyte to monocyte ratio; NPS= Naples prognostic score, calculated by including the value of serum albumin, total cholesterol, NLR and LMR.

[a] 95% confidence interval
[b] median value
[c] according to the Bormann's classification
[d] TNM stage according to the AJCC 8th edition (reference n. 1)
[e] cut-off value was determined by using R MaxStat analysis
[f] NPS0 includes patients whose NPS score was 0; NPS1 includes patients whose NPS score was 1 or 2; NPS2 includes patients whose NPS score was > 2

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TABLE II - *Clinico-pathological characteristics and univariate and multivariate analyses of disease-free survival rates in 307 patients with gastric cancer who underwent potentially curative surgery*

			Univariate Analyses			Multivariate Analyses		
Factor	**Nr. Pts**	**% 5-years DFS**	**HR**	**95%CI HR a**	**P value**	**HR**	**95%CI HR a**	**P value**
Age [b]								
< 65 years	172	53.9	1	Referent	0.342	//	//	//
> 65 years	135	50.7	1.17	0.83-1.65				
Gender								
Male	183	58.7	1	Referent	0.038	1	Referent	0.286
Female	124	43.4	1.43	1.02-2.01		1.40	0.75-2.60	
CEA								
< 3.5 ng/mL	234	54.5	1	Referent	0.039	1	Referent	0.005
> 3.5 ng/mL	73	45.3	1.47	1.01-2.12		2.23	1.27-3.92	
CA19-9								
< 37 U/mL	233	56.1	1	Referent	0.013	1	Referent	0.200
> 37 U/mL	74	40.3	1.58	1.10-2.28		1.01	0.86-1.23	
PS								
0	122	62.1	1	Referent	0.008	1	Referent	0.425
1/2	185	45.7	1.62	1.13-2.33		1.24	0.72-2.15	
Tumor Site								
Distal	124	58.2	1	Referent	0.088	1	Referent	0.003
Middle Third	104	50.6	1.37	0.91-2.06		3.04	1.60-5.78	
Upper Third	79	45.3	1.58	1.03-2.42		1.21	0.66-2.23	
PreOP Ch.								
Yes	36	67.9	1	Referent	0.903	//	//	//
No	271	52.1	1.04	0.54-1.99				
Macroscopic Type [c]								
Mass	53	71.9	1	Referent		1	Referent	
Ulcerative	122	62.9	1.72	0.91-3.26	0.001	0.83	0.31-2.21	0.823
Ulcerative infiltrative	108	35.6	2.98	1.61-5.53		1.05	0.41-2.65	
Diffuse infiltrative	24	27.1	2.94	1.34-6.45		0.82	0.22-3.02	
Histological Type								
Differentiated	177	59.3	1	Referent	0.011	1	Referent	0.124
Undifferentiated	130	41.6	1.55	1.10-2.18		1.83	0.84-3.99	
Lauren's classification								
Intestinal	168	59.6	1	Referent	0.004	1	Referent	0.227
Diffuse	139	43.4	1.64	1.16-2.30		1.62	0.74-3.55	
PO Complic.								
No	238	58.6	1	Referent	<0.001	1	Referent	<0.001
Yes	69	31.0	2.75	1.92-3.93		3.11	1.78-5.42	
PO Ch.								
No	113	59.3	1	Referent	0.368	//	//	//
Yes	194	48.8	1.18	0.82-1.69				
TNM stage [d]								
IA	70	93.9	1	Referent		1	Referent	
IB	38	62.2	4.19	1.57-11.19		1.50	1.30-1.74	
IIA	50	52.0	6.64	2.69-16.41		16.54	4.53-60.37	
IIB	75	34.8	10.55	4.50-24.72	<0.001	12.40	3.69-41.61	<0.001
IIIA	37	34.7	9.06	3.58-22.90		12.45	3.90-39.79	
IIIB	21	0.0	19.31	7.60-49.06		13.27	3.92-44.84	
IIIC	13	21.2	20.08	6.94-58.3		43.53	11.27-68.57	
IV	3	0.0	72.40	43.09-98.92		31.71	7.47-74.57	
Albumin								
> 4 g/dL	199	62.4	1	Referent	<0.001	1	Referent	0.254
< 4 g/dL	108	35.0	2.05	1.46-2.87		1.40	0.78-2.52	
Cholesterol								
> 180 mg/dL	172	64.5	1	Referent	<0.001	1	Referent	0.715
< 180 mg/dL	135	37.3	2.38	1.69-3.37		1.14	0.54-2.42	
Lymphocytes								
> 1600 mm^3	161	64.5	1	Referent	<0.001	1	Referent	0.062
< 1600 mm^3	146	38.3	1.95	1.38-2.76		1.78	0.97-3.29	

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Table II - *Clinico-pathological characteristics and univariate and multivariate analyses of disease-free survival rates in 307 patients with gastric cancer who underwent potentially curative surgery*

			Univariate Analyses			Multivariate Analyses		
Factor	**Nr. Pts**	**% 5-years DFS**	**HR**	**95%CI HR a**	**P value**	**HR**	**95%CI HR a**	**P value**
NLR [e]								
< 3.22	223	63.8	1	Referent	<0.001	1	Referent	0.085
> 3.22	84	21.9	3.01	2.13-4.25		1.91	0.91-4.03	
LMR [e]								
> 3.48	191	66.8	1	Referent	<0.001	1	Referent	0.246
< 3.48	116	29.4	2.84	2.02-4.01		2.01	0.61-6.60	
PNI [e]								
> 49	197	65.6	1	Referent	<0.001	1	Referent	0.850
< 49	110	30.5	2.58	1.84-3.63		1.10	0.39-3.13	
CONUT [e]								
< 1	194	68.3	1	Referent	<0.001	1	Referent	0.325
> 1	113	21.5	3.48	2.46-4.92		1.46	0.68-3.16	
SIS								
0	117	66.0	1	Referent	<0.001	1	Referent	0.317
1	106	58.7	1.17	0.75-1.81		1.02	0.15-6.44	
2	84	26.7	2.61	1.72-3.96		0.63	0.22-1.79	
NPS group [f]								
0	69	76.0	1	Referent	<0.001	1	Referent	0.009
1	156	59.1	1.70	0.98-2.96		3.71	1.34-10.21	
2	82	20.2	4.98	2.85-8.68		14.48	2.61-30.23	

HR= hazard ratio; CEA= carcinoembryonic antigen (normal level 3.5 ng/mL); CA19-9= carbohydrate antigen 19-9 (normal level 37 U/mL); PS= performance status according to the ECOG scale; PreOP Ch.= preoperative chemotherapy; PO Complic.= postoperative complications defined as grade II or higher of the Clavien-Dindo classification (reference n. 29); PO Ch=postoperative chemotherapy; NLR= neutrophil to lymphocyte ratio; LMR= lymphocyte to monocyte ratio; PNI= prognostic nutritional index, calculated as follows: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count in the peripheral blood; CONUT= controlling nutritional status, a scoring system calculated by summing the value of serum albumin, total cholesterol, and total lymphocyte count in the peripheral blood; SIS= system inflammation score based on serum albumin and lymphocyte to monocyte ratio; NPS= Naples prognostic score, calculated by including the value of serum albumin, total cholesterol, NLR and LMR.

[a] 95% confidence interval
[b] median value
[c] according to the Bormann's classification
[d] TNM stage according to the AJCC 8th edition (reference n. 1)
[e] cut-off value was determined by using R MaxStat analysis
[f] NPS0 includes patients whose NPS score was 0; NPS1 includes patients whose NPS score was 1 or 2; NPS2 includes patients whose NPS score was > 2

Table III - *Comparison of the prognostic performance of the four scoring systems*

	NPS	**SIS**	**CONUT**	**PNI**
A) Overall Survival (n=415 patients)				
Likelihood Ratio [a]	47.65	25.04	44.73	39.81
Linear Trend [b]	45.64	24.42	42.96	38.32
B) Disease-free Survival (n=307 patients)				
Likelihood Ratio[a]	44.24	21.26	38.86	33.42
Linear Trend[b]	43.47	18.97	35.54	33.03

[a] chi-square test; higher values show better homogeneity (small difference in OS or DFS rate among patients classified into the same group by that system)
[b] chi-square test; higher values mean monotonicity (the OS or DFS rates in a more favorable stage are always higher than the OS or DFS rates in a worse stage)

NPS= Naples prognostic score, calculated by including the value of serum albumin, total cholesterol, neutrophil to lymphocyte ratio, and lymphocyte to monocyte ratio; SIS= system inflammation score, developed based on serum albumin and lymphocyte to monocyte ratio; CONUT= controlling nutritional status, a scoring system calculated by summing the value of serum albumin, total cholesterol, and total lymphocyte count in the peripheral blood; PNI= prognostic nutritional index, calculated as follows: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count in the peripheral blood.

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viously developed prognostic systems, NPS displayed the best prognostic performance, matching the TNM staging system. Finally, this study is the first NPS validation, after its initial implementation in colorectal cancers where NPS performed as the best scoring system .[26] Gastric cancer remains a worldwide challenge with disappointing long-term results mainly due to predisposition of this tumor to locally recur and metastasize. Therefore, identification of patients with high risk of recurrence through clinically useful markers appears fundamental for sound strategies [27]. Recently, host characteristics, particularly inflammatory and immune-nutritional status, have been suggested to be crucial for tumor growth and cancer progression [7,8]. A number of candidate biomarkers has been investigated in the hope of gaining preventive insights into cancer behavior. Indeed, an optimal prognostic score must include inexpensive, readily available, and reliable prognostic markers capable of summarizing the main characteristics of the host [37]. However, currently investigated prognostic systems have had little diffusion due to inclusion of a limited number of biomarkers, different cutoff values, and lack of robust statistical methods [19]. In addition, very few studies have been carried out in gastric cancer patients. On these premises, we developed a prognostic score including variables capable of reflecting both immune-nutritional and inflammatory host status. NPS includes serum levels of albumin and total cholesterol that are known to be important markers of malnutrition but also of systemic inflammation [33,38]. Indeed, hypoalbuminemia and hypocholesterolemia reflect malnutrition, however, at the same time, albumin and cholesterol concentrations may be reduced by pro-inflammatory substances, such as cytokines [31,39,40]. In addition, NLR and LMR demonstrated to be the best candidates to mirror inflammatory and immune status [7,37]. Neutrophilia reflects inflammation while lymphocytes are essential for host immune system to recognize and eliminate cancer cells [41]. Consistently, an elevated NLR has been shown to correlate with worse outcome in several human tumors including gastric cancer [17,42]. Monocytes differentiate into tumor-associated macrophages within cancer microenvironment, where they may encourage tumor progression, angiogenesis and metastases [43]. A low LMR has been shown to inversely correlate with prognosis in some human tumors [25,32,34]. To date, only four studies have investigated the role of LMR in gastric cancer, with interesting results [9-11,22].

The most important issues with prognostic score systems are represented by both the cutoff values and their cor-

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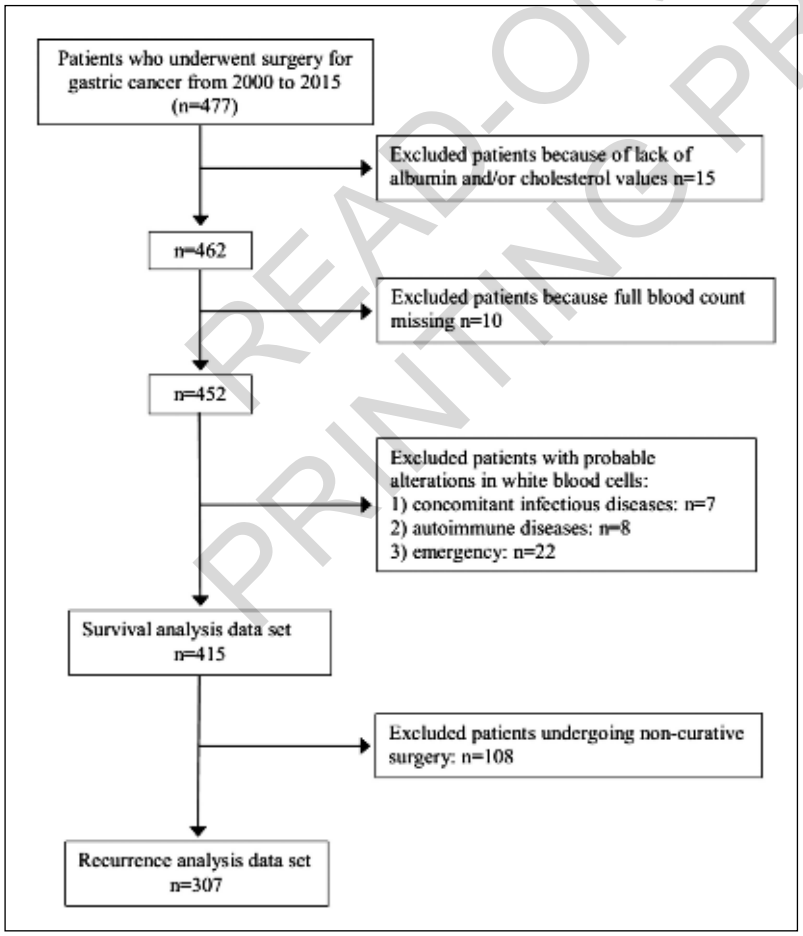

Fig. 1: Flow diagram of the analyzed cases.

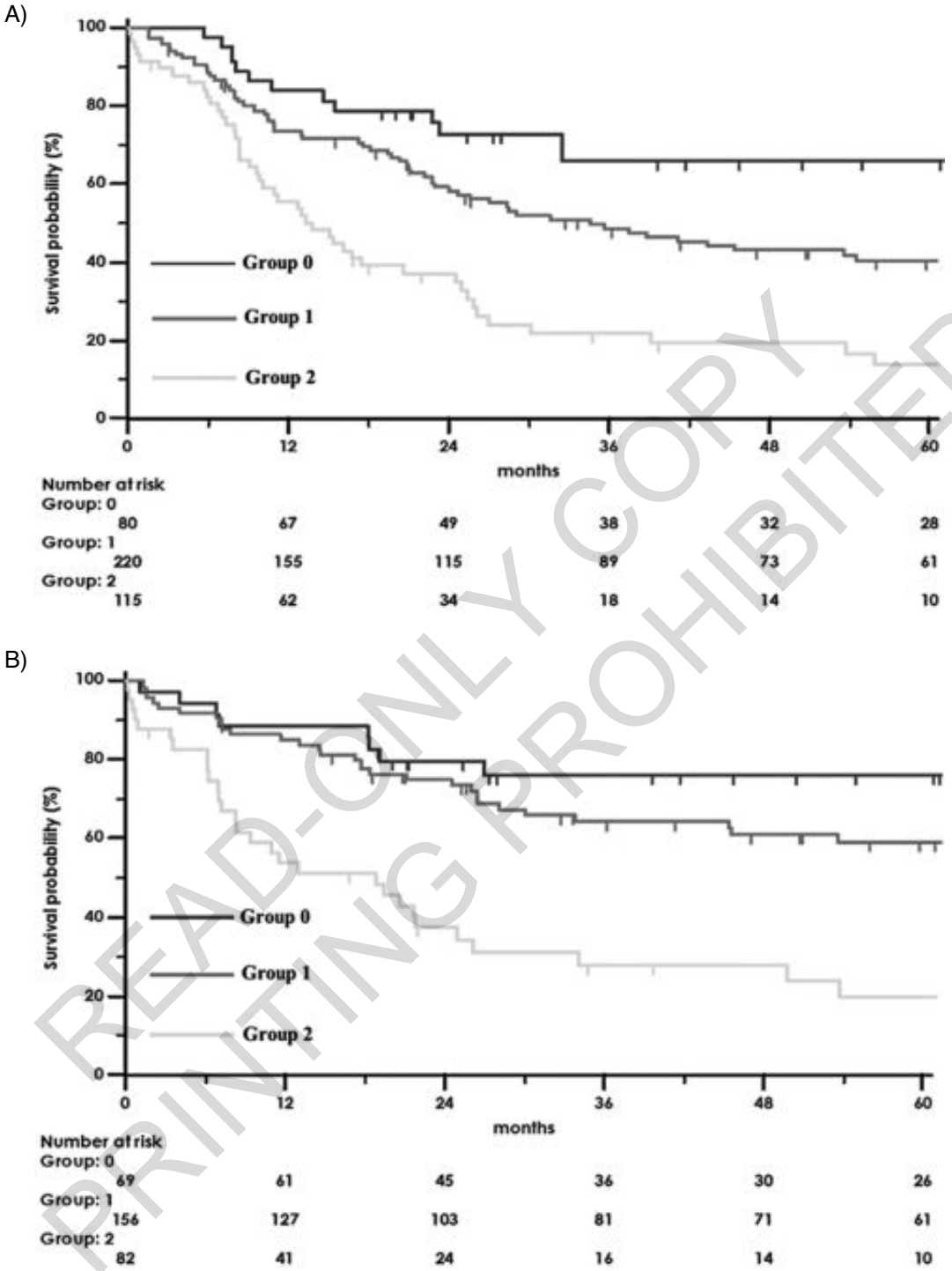

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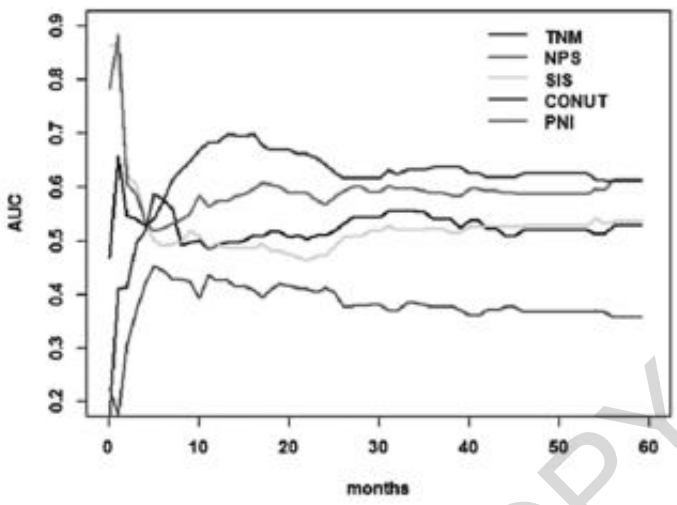
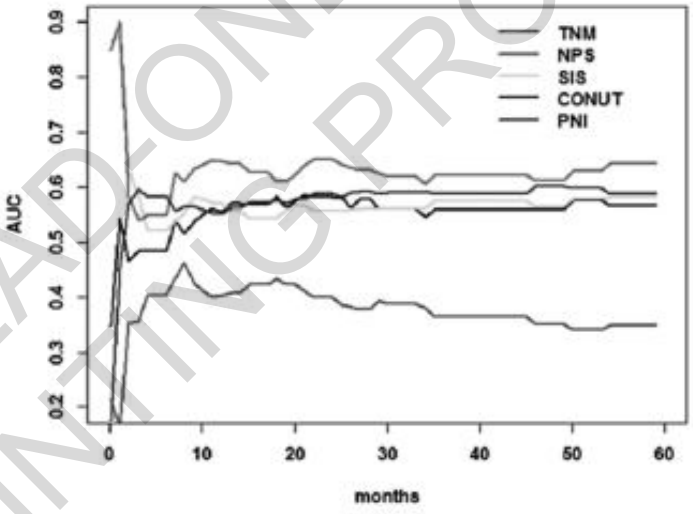
Fig. 2:
A) Overall survival rates in 80 patients (group 0) grouped as NPS=0, 220 patients (group 1) grouped as NPS=1, and 115 patients (group 2) grouped as NPS=2, who underwent surgery for gastric cancer.
(NPS1 hazard ratio (HR) = 2.04 (95% confidence interval (CI), 1.33-3.14); NPS2 HR = 4.27 (95% CI, 2.73-6.66); $p < 0.001$). .
B) Disease-free survival rates in 69 patients (group 0) grouped as NPS=0, 156 patients (group 1) grouped as NPS=1, and 82 patients (group 2) grouped as NPS=2, who underwent potentially curative surgery for gastric cancer.
(NPS1 HR = 1.70 (95% CI, 0.98-2.96); NPS2 HR = 4.98 (95% CI, 2.85-8.68); $p < 0.001$)

A)



	1 month	12 months	24 months	36 months	48 months	60 months
TNM	0.405	0.689	0.646	0.639	0.624	0.607
NPS	0.881	0.573	0.571	0.592	0.588	0.616
SIS	0.868	0.480	0.484	0.534	0.538	0.545
CONUT	0.656	0.493	0.515	0.542	0.518	0.525
PNI	0.173	0.424	0.410	0.375	0.367	0.355

B)



	1 month	12 months	24 months	36 months	48 months	60 months
TNM	0.448	0.557	0.604	0.597	0.609	0.593
NPS	0.900	0.648	0.652	0.622	0.612	0.649
SIS	0.875	0.577	0.559	0.576	0.565	0.583
CONUT	0.590	0.561	0.589	0.561	0.561	0.566
PNI	0.162	0.405	0.399	0.364	0.350	0.349

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Fig. 3. Analysis of the predictive accuracy of different score systems through months of follow-up, computed by time-dependent receiver operating characteristic analysis for censored survival data. The horizontal axis and the vertical axis represent months after surgery and the estimated area under the curve (AUC), respectively. The tables under the graphics report AUC values for each staging system.
A) Overall survival (415 patients who underwent surgery for gastric cancer).
B) Disease-free survival (307 patients who underwent potentially curative surgery for gastric cancer).

relations with other negative predictive factors that might either obscure or alter their influence. We used the MaxStat analysis to individuate the optimal cutoff value for different biomarkers [22,26]. This statistical method, based on exact asymptotic distributions, iteratively tests all possible cutpoints until the selected value corresponds to the largest discrepancy between the lower and higher risk groups based on log-rank statistics, while controlling for multiple variables [34]. In the formulation of this study, we decided to calculate NPS by leaving unaltered the cutoff values used in colorectal cancers [26]. Interestingly, cutoff values for NLR and LMR, computed by MaxStat analysis, were 3.22 and 3.48, respectively; these values were really close to those used for NPS computation (2.96 and 4.44, respectively). Besides, these values were quite similar to those selected in previous gastric cancer studies [9-11,24].

This study has some limitations. First, it was a single-center study; however, selection bias was nonetheless reduced by the large, prospectively collected series of consecutive patients. Second and most importantly, validity and generazibility of these results need to be established by testing the score in different geographic locations and groups of patients [44].

NPS correlation with morbidity and outcome in gastric cancer patients may have important clinical implications both in pre- and postoperative settings. Accurate clinical stage evaluation is crucial to decide on neoadjuvant therapy, since understaging excludes patients who could benefit from it, while overstaging exposes to the morbidity of chemotherapy [27]. Unfavorable NPS scores could be used to recommend neoadjuvant therapy in patients judged borderline with current imaging techniques [22,45]. In addition, early detection and improvement of malnutrition and inflammation may result in better patient outcomes and prevention of postoperative complications [33,46,47]. Currently, we are investigating this tool in our colorectal and gastric cancer patient populations in order to preoperatively improve status in altered NPS subjects [22,26].

In conclusion, preoperative NPS is a simple, easily obtainable scoring system, which has been shown to be strongly associated with outcome in almost 1000 oncological patients undergoing surgery, including 415 gastric and 562 colorectal cancers. Patients with altered preoperative NPS values should be deemed at high risk for tumor relapse and considered for tailored therapy. Further independent validation is needed to conclusively address this issue and to determine whether this strategy may be rewarding in the long-term.

Riassunto

SCOPO: In molte neoplasie umane è stato dimostrato che il decorso della malattia oncologica non dipende solo dallo stadio del tumore ma anche dalle condizioni del paziente, in particolare lo stato nutrizionale, immunologico ed infiammatorio. Nel cancro dello stomaco, comunque, le esperienze sono ancora limitate. Lo scopo principale di questo studio è stato di valutare prospetticamente un nuovo sistema prognostico (definito Naples Prognostic Score – NPS), e di confrontarlo con precedenti sistemi già studiati come il PNI (Prognostic Nutritional Index), il CONUT (Controlling Nutritional Status), e il Systemic Inflammation Score (SIS).

METODI: Sono state calcolate le percentuali di sopravvivenza globale (OS) e di complicanze in 415 pazienti sottoposti a chirurgia per tumore dello stomaco dal gennaio 2000 al dicembre 2015. Le percentuali di sopravvivenza libera da malattia (DFS) sono state valutate in 307 pazienti sottoposti a chirurgia potenzialmente curativa. Il sistema statistico MaxStat è stato utilizzato per identificare i migliori valori soglia dei differenti biomarcatori, ed i punteggi dell'NPS sono stati divisi in 3 gruppi (NPS 0-3). L'efficacia prognostica dei differenti sistemi di punteggio considerati è stata investigata mediante una sofisticata tecnica statistica costituita dalla Receiver-Operating-Characteristic (ROC) Curve per i dati di sopravvivenza censurati.

RISULTATI: Il nuovo sistema prognostico NPS ha dimostrato possedere una positiva correlazione statistica con i precedenti sistemi (p <0,001), e gli stadi avanzati del tumore (p <0,001). Nei pazienti con punteggi più alti di NPS sono state osservate un maggior numero di complicanze postoperatorie (tutti i pazienti: p = 0,003; pazienti trattati radicalmente: p = 0,010). Rispetto ai pazienti con un punteggio uguale a 0 di NPS, i pazienti con valori di NPS uguali a 1 o 2 hanno mostrato un rischio maggiore (HR) di presentare una sopravvivenza globale minore (NPS1 HR 2,04, NPS2 HR 4,27; p <0,001), ed un più breve decorso libero da recidiva neoplastica (NPS1 HR 1,70, NPS2 HR 4,98; p <0,001). Tra i diversi sistemi di punteggio, solo l'NPS è stato selezionato come un fattore prognostico significativamente indipendente per OS (p = 0.024) e DFS (p = 0.009). L'analisi ROC ha evidenziato che l'NPS ha dimostrato possedere, tra i quattro sistemi analizzati, la migliore capacità prognostica nell'identificare i pazienti ad alto rischio di recidiva neoplastica, ed ha quasi eguagliato l'attuale sistema di stadiazione TNM.

CONCLUSIONI: Il Naples Prognostic Score è un sistema prognostico facile da calcolare, ed appare essere positivamente correlato ai risultati oncologici nei pazienti sottoposti a chirurgia per cancro dello stomaco.

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