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Prognostic value of neutrophil–lymphocyte ratio and level of C-reactive protein in a large cohort of pancreatic cancer patients: a retrospective study in a single institute in Japan

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Abstract

Objective: Recent studies suggest that systemic inflammatory response is closely associated with cancer patient prognosis. Although several inflammatory prognostic markers have been proposed, the data to support their validity are lacking in large Japanese cohorts.

Methods: This is a retrospective study to examine the prognostic value of inflammatory markers, such as C-reactive protein, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio and modified Glasgow prognostic scale, in pancreatic cancer. Selection criteria were admittance to hospital between January 2008 and December 2012, histologically confirmed adenocarcinoma, diagnosis of invasive ductal pancreatic cancer compatible by computed tomography imaging, and followed-up until death or for 180 days or longer. The primary end point was overall survival, which was measured from the day of histological diagnosis.

Results: There were 440 patients who met the selection criteria. Of the 440 cases, 200 (45.5%) received curative resection (166 Stage I/II and 34 Stage III patients), 237 (53.9%) received chemotherapy (4 Stage I/II, 92 Stage III and 141 Stage IV patients), and the remaining 3 received palliative care. Univariate and multivariate regression analyses revealed that advanced computed tomography stage, high level of C-reactive protein (0.45 mg/dl or greater), neutrophil–lymphocyte ratio (2.0 or greater) and CA19-9 level (1000 U/ml or greater) were significantly associated with worse prognosis.

Conclusions: We verified the results of previous studies, and showed that neutrophil–lymphocyte ratio and C-reactive protein also had prognostic value in a large Japanese PC cohort.

Key words: NLR, CRP, mGPS, PLR, survival

Introduction

Pancreatic cancer (PC) has become the fifth most common cause of cancer-related mortality in Japan; it has been estimated that PC was responsible for 29 916 deaths in 2012 (1), representing ~8% of all cancer deaths. Despite recent improvements in diagnostic techniques, only a small proportion of patients are eligible for surgery, even though resection represents the only curative treatment available thus far. Accordingly, the prognosis of PC patients is extremely poor, with a 5-year survival rate after diagnosis of <5% (2).

Recent studies suggest that the systemic inflammatory response is closely associated with cancer patient prognosis (3,4). Several parameters of the systemic inflammatory response, including level of C-reactive protein (CRP), neutrophil–lymphocyte ratio (NLR), derived NLR (dNLR), platelet–lymphocyte ratio (PLR) and modified Glasgow prognostic score (mGPS), have been demonstrated in numerous reports as good prognostic indicators in lung cancer (5), hepatocellular carcinoma (6), melanoma (7), renal cell carcinoma (8), gastric cancer (9) and colorectal cancer (10). Moreover, some studies have shown that these parameters can predicted clinical outcome in regardless of the primary site (11,12).

Further, initial reports have already indicated that the inflammatory response is predictive of prognosis in patients with PC, but most of these studies included only relatively small number of cases (13–17). An Austrian group has reported the prognostic value of NLR, dNLR and CRP as useful inflammatory markers in their large cohort of PC patients (18–20). In the present study, we aimed to validate the prognostic significance of inflammatory markers in a large cohort of Japanese PC patients with reference to the Austrian studies.

Patients and methods

This retrospective study included data from 493 consecutive patients who were diagnosed with PC at the Gastroenterology Center, Cancer Institute Hospital of Japanese Foundation for Cancer Research between January 2008 and December 2012. Among these 493 patients, we selected those for the current study if all of the following criteria were met: (i) histologically or cytologically confirmed adenocarcinoma, (ii) invasive ductal PC compatible by computed tomography (CT) imaging and (iii) followed-up until death or for 180 days or longer.

Clinical variables collected in this study were: age, gender, height, weight and performance status (PS) according to the Eastern Cooperative Oncology Group grading system; white blood cell (WBC) count; fraction of neutrophil and lymphocyte in WBC differentiation (%); levels of albumin, bilirubin, CRP and carbohydrate antigen 19-9 (CA19-9); location of the primary pancreatic tumor; clinical CT stage according to the seventh edition of TNM classification; type of therapy (i.e. tumor resection, chemotherapy or symptomatic treatment); date of surgical intervention or biopsy and date of the final follow-up or death. The baseline data were obtained within 30 days prior to surgical intervention or biopsy.

The relationship between each baseline variable and long-term survival was investigated by univariate and multivariate analyses, with special focus on the prognostic impact of systemic inflammation markers. On the basis of previous studies, CRP level of 0.45 mg/dl, NLR of 2.0, dNLR (absolute count of neutrophils divided by the absolute WBC count minus the absolute count of neutrophils) of 2.3 and PLR of 150 were selected as cutoff values for validation. The mGPS was applied by combining CRP and albumin levels: 0 was defined as normal values of CRP and albumin; 1 was defined as increased CRP (1.0 mg/dl or greater) and normal albumin; and 2 was defined as increased CRP and decreased albumin (<3.5 g/ml). Other than the five inflammatory markers, variables included in the prognostic analysis were: age (65 years or younger versus older than 65); gender; PS (0 versus 1); body mass index (>25 versus 25 or greater); location of the primary tumor (head versus body–tail); clinical CT Stage (I/II, III or IV); and CA 19-9 (>1000 U/ml versus 1000 U/ml or greater).

The primary end point of this study was overall survival (OS), defined as the time from the date of histological confirmation (the date of surgery or biopsy) to death due to any cause or to the last known date alive. All patients were assessed in December 2013. Kaplan–Meier survival plots were generated, and differences in survival among subgroups classified by each factor were evaluated by log-rank tests. Cox regression was used to determine univariate hazard ratios for OS. Age, PS and all variables with significant prognostic value in the univariate analysis were selected for further evaluation in the final multivariate Cox proportional hazard model. Multivariate Cox proportion analysis by backward elimination method was performed to determine the influence of the different variables on OS. Hazard ratios estimated by the Cox analysis were reported as relative risks with corresponding 95% confidence intervals. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the PASW Statistics 18 program (SPSS Inc., Chicago, IL, USA).

The Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research approved this study, and waived the need for written informed consent from the participants because this was a retrospective non-intervention study.

Results

Of the 493 patients, 440 met the selection criteria. Of the remaining 53, 28 had other tumor histologies including neuroendocrine tumor, and 25 were transferred to a community hospital to receive palliative care within 6 months after diagnosis. Patient characteristics are summarized in Table 1. Of the 170 patients diagnosed with Stage I/II potentially resectable disease, 4 received chemotherapy because micro-metastases were found by laparotomy. Of the 127 patients diagnosed with Stage III disease, 34 underwent resection of the pancreas, 92 received chemotherapy and the remaining 1 received symptomatic treatment. Of the 143 patients diagnosed with Stage IV disease, 141 received chemotherapy and the remaining 2 received symptomatic treatment. Consequently, 200 (45.5%) patients received curative resection (166 Stage I/II and 34 Stage III cases), 237 (53.9%) received chemotherapy (4 Stage I/II, 92 Stage III and 141 Stage IV patients) and the remaining 3 received palliative care. Of the 440 selected patients, 313 (71.1%) died and the remaining 127 were still alive at the time of analysis. The median follow-up time of the 127 survivors was 18.7 months, ranging from 6.1 to 68.2 months. The median survival time of patients from the whole cohort was 11.6 months (interquartile range: 7.1–20.1 months).

Univariate Cox regression revealed that advanced CT stage, pancreatic body–tail cancer, high level of CRP, NLR, dNLR and CA19-9 level were significantly associated with worse prognosis (Table 2). We continued to analyze NLR but not dNLR in the multivariate analysis because the hazard ratio of NLR was higher than that of dNLR (1.894 versus 1.576, respectively). PLR and mGPS did not show any evident prognostic impact on survival in our cohort. In the multivariate analysis, CT stage, level of CRP, NLR and CA19-9 level were identified as independent prognostic factors in our cohort (Table 3).

Figure 1 demonstrates OS curves stratified by NLR in each CT stage, respectively. The number of patients with NLR >2.0 and those with NLR ≥2.0 were 71 (41.8%) and 99 (58.2%) in Stage I/II, 48 (37.8%) and 79 (62.2%) in Stage III and 21 (14.7%) and 122 (85.3%) in Stage IV. The prognostic value of NLR was clear especially in CT Stage I/II disease ($P = 0.014$, log-rank test). But there was no significant difference between Stages III and IV ($P = 0.079$ and $P = 0.125$).

Figure 2 demonstrates OS curves stratified by CRP in each CT stage, respectively. The number of patients with CRP <0.45 and

Table 1. Patient characteristics

Age (years)		
Median (range)	67	32–88
65 or younger	179	40.7%
Older than 65	261	59.3%
Gender		
Male	249	56.6%
Female	191	43.4%
Performance status		
0	378	83.3%
1	62	13.7%
Body mass index		
Median (range)	21.6	13.0–33.8
<25	375	85.2%
25 or greater	65	14.8%
Location of the primary tumor		
Head	220	50.0%
Body–tail	220	50.0%
Clinical CT stage		
I/II	170	38.6%
III	127	28.9%
IV	143	32.5%
C-reactive protein (mg/dl)		
Median (range)	0.12	0.01–21.9
<0.45	321	73.0%
0.45 or greater	119	27.0%
Neutrophil–lymphocyte ratio		
Median (range)	2.47	0.7–27.7
<2	140	31.8%
2 or greater	300	68.2%
Derived neutrophil–lymphocyte ratio		
Median (range)	1.77	0.5–13.3
<2.3	324	73.6%
2.3 or greater	116	26.4%
Platelet–lymphocyte ratio		
Median (range)	140.0	40.4–930.8
<150	239	54.3%
150 or greater	201	45.7%
Modified Glasgow prognostic score		
0	367	83.4%
1	49	11.1%
2	24	5.5%
Albumin (g/dl)		
Median (range)	4.0	2.4–5.0
<3.5	48	10.9%
3.5 or greater	392	89.1%
CA19-9 (U/ml)		
Median (range)	436.2	2.0–50 000
<1000	275	625%
1000 or greater	165	37.5%

those with CRP ≥0.45 were 147 (86.5%) and 23 (13.5%) in Stage I/II, 102 (80.3%) and 25 (19.7%) in Stage III and 72 (50.3%) and 71 (49.7%) in Stage IV, respectively. The prognostic value of CRP was evident in CT Stage III and IV disease ($P = 0.015$ and $P < 0.001$).

Figure 3 shows box plots of CRP and NLR in each CT stage. The dotted line means the cutoff level. The fraction of patients with NLR under the cutoff level was small especially in Stage IV, whereas most patients in Stage I/II had lower CRP level than the cutoff level.

Figure 4 demonstrates plots of the cumulative distribution function of NLR and CRP. The degree of asymmetric distribution of CRP was larger than that of NLR, with skewness coefficients of 5.568 and 4.803, respectively.

Table 2. Univariate cox regression

	HR	95% CI	*P* value
Age			
65 or younger	1		
Older than 65	0.806	0.644–1.008	0.059
Gender			
Male	0.985	0.788–1.232	0.897
Female	1		
Performance status			
0	1		
1	1.261	0.924–1.720	0.143
Body mass index			
<25	1		
25 or greater	1.192	0.883–1.609	0.252
Location of the primary tumor			
Head	1		
Body–tail	1.499	1.199–1.873	<0.001
Clinical CT stage			
I/II	1		
III	2.225	1.666–2.972	<0.001
IV	5.351	3.996–7.166	<0.001
C-reactive protein (mg/dl)			
1			
0.45 or greater	2.323	1.820–2.966	<0.001
Neutrophil–lymphocyte ratio			
<2.0	1		
2.0 or greater	1.894	1.474–2.435	<0.001
Derived neutrophil–lymphocyte ratio			
<2.3	1		
2.3 or greater	1.576	1.234–2.012	<0.001
Platelet–lymphocyte ratio			
<150	1		
150 or greater	1.048	0.838–1.309	0.683
Modified Glasgow prognostic score			
0	1		
1	2.61	1.89–3.605	<0.001
2	1.465	0.906–2.369	0.119
Albumin (g/dl)			
<3.5	1		
3.5 or greater	1.161	0.801–1.683	0.431
CA19-9 (U/ml)			
<1000	1		
1000 or greater	2.002	1.591–2.519	<0.001

HR, hazard ratio; CI, confidence interval.

Discussion

Previous studies suggest that disease progression in cancer patients is not only driven by the intrinsic properties of tumor cells, but also by systemic host reactions. Some systemic factors, in the shape of cytokines and other chemical messengers, may play an important role in cellular proliferation and metastatic ability (3,4). Although the detailed mechanisms have not been fully elucidated yet, several markers that reflect systemic inflammation have been reported to be closely associated with patient prognosis in different types of cancer (5–12). Among these inflammatory factors, we tested level of CRP, NLR, dNLR, PLR and mGPS in a large Japanese PC cohort in the current study. An Austrian group had already reported that NLR (18), dNLR (19) and CRP (20) predicted clinical outcome, and our study aimed to validate their findings. As a result, we confirmed that NLR and CRP have prognostic value in a large Japanese cohort similar to the Austrian studies. On the other hand, PLR and mGPS did not

Table 3. Multivariate cox regression

	HR	95% CI	*P* value
Age			
65 or younger	1		
Older than 65	0.834	0.665–1.045	0.115
Performance status			
0	1		
1	1.284	0.923–1.788	0.138
Location of the primary tumor			
Head	1		
Body–tail	1.07	0.842–1.359	0.582
Clinical CT stage			
I/II	1		
III	2.191	1.638–2.931	<0.001
IV	4.141	3.035–5.648	<0.001
C-reactive protein (mg/dl)			
<0.45	1		
0.45 or greater	1.695	1.308–2.197	<0.001
Neutrophil–lymphocyte ratio			
<2.0	1		
2.0 or greater	1.404	1.078–1.830	0.012
CA19-9 (U/ml)			
<1000	1		
1000 or greater	1.435	1.127–1.826	0.003

demonstrate any prognostic value in our cohort, possibly due to ethnic difference and/or specificity of cancer type.

As compared with the Austrian cohort, there were more patients with earlier stage disease in our cohort. The fraction of Stage IV patients was 70% in the Austrian studies and 33% in this report. The mean values of NLR and CRP were 4.75 and 2.32 mg/dl, respectively, in the Austrian reports, and 3.06 and 0.80 mg/dl, respectively, in the current one. The median survival time and interquartile range were 7 and 3–17 months, respectively, in the Austrian cohort, and 11.6 and 7.1–20.1 months, respectively, in ours. Due to a high surgeon volume in our institute, we fortunately had an advantage in recruiting many PC patients with earlier stage. In any case, the important fact was that the prognostic impacts of NLR and CRP were confirmed in resectable and unresectable PC patients, respectively, in both European and Asian cohorts.

Although we verified the prognostic value of NLR and CRP in PC patients, there were differences between the characters of NLR and CRP as prognostic markers. One important point is that NLR is a relative value. Because a neutrophil count of zero is not a realistic situation, thus, NLR cannot approach zero (Fig. 4). Figure 3 shows the distribution of NLR and CRP in each clinical stage. The level of NLR tended to become higher as the clinical stage progressed. Accordingly, the cutoff level of 2.0 was appropriate for resectable disease but

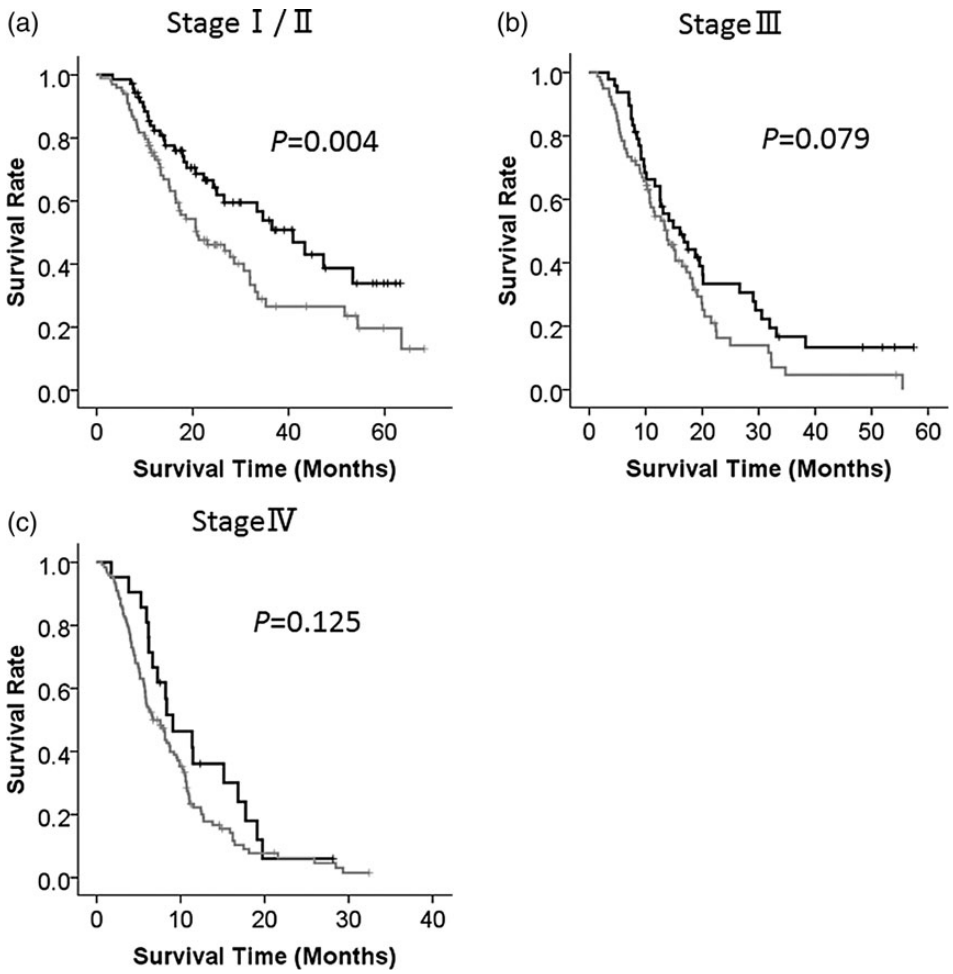

Figure 1. Overall survival curves stratified by neutrophil–lymphocyte ratio (NLR) for Stage I/II (a), Stage III (b) and Stage IV (c). Vertical lines represent censoring of data. Black and gray lines indicate subgroup of patients with NLR <2.0 and those with NLR ≥2.0, respectively. Prognosis of patients with increased NLR was significantly poorer in Stage I/II ($P = 0.004$, log-rank test).

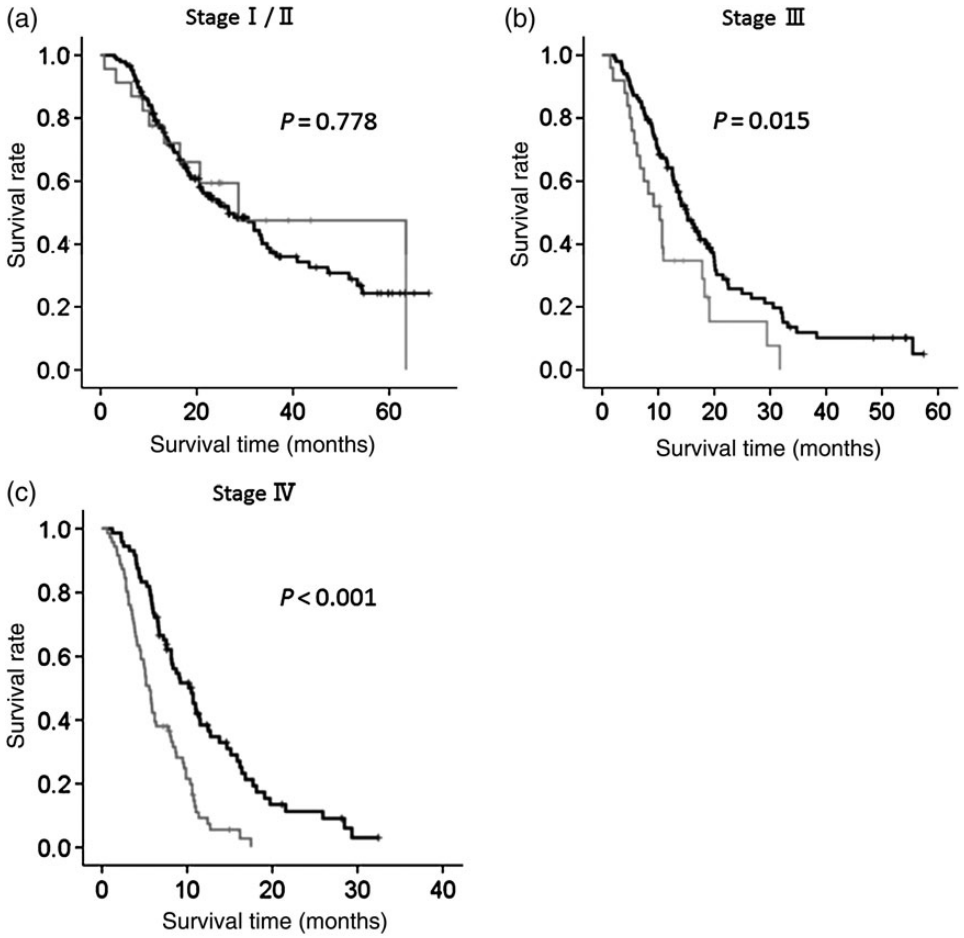

Figure 2. Overall survival curves stratified by C-reactive protein (CRP) for Stage I/II (a), Stage III (b) and Stage IV (c). Vertical lines represent censoring of data. Black and gray lines indicate subgroup of patients with CRP <0.45 and those with CRP ≥0.45, respectively. Prognosis of patients with increased CRP was significantly poorer in Stage III ($P = 0.015$) and Stage IV ($P < 0.001$, log-rank test).

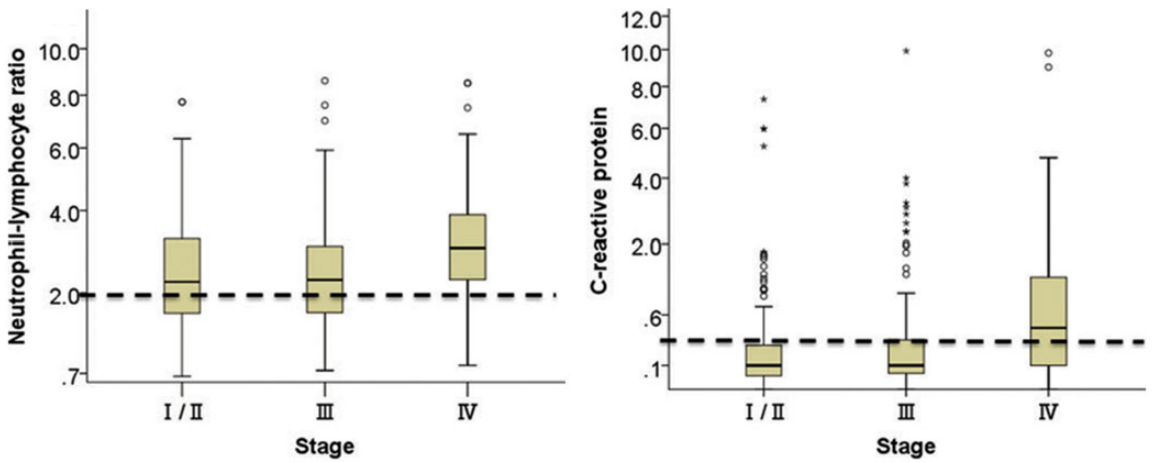

Figure 3. Box plots of CRP and NLR stratified by clinical stage. The dotted line denotes the cutoff level. The fraction of patients with NLR under the cutoff level was small especially in Stage IV, whereas most patients in Stage I/II had lower CRP level than the cutoff level.

it was too low to show the statistical significance in unresectable disease. If the cutoff level of NLR was set separately in each clinical stage, the prognostic value of NLR would be evident in both resectable and unresectable diseases. In practice, when we applied the cutoff level of 5.0 for NLR, the result was opposite from the result mentioned above, namely, the prognostic value of NLR was evident in unresectable disease, but not evident in resectable disease. On the other hand, CRP level is an absolute value, and small values close to zero represent a normal condition in general. To determine the cutoff level of CRP for patients especially in early stage was difficult because almost all

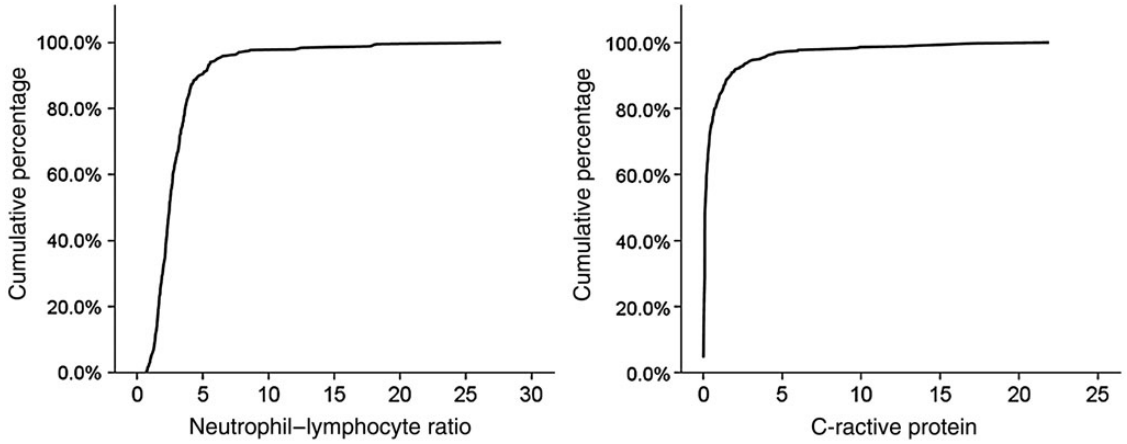

Figure 4. Cumulative distribution function plots of NLR and CRP. NLR cannot approach zero (95% of the NLR in our cohort were distributed between 1.1 and 6.2). On the contrary, small CRP values close to zero represent a normal condition. In the present study, 74% of the CRP levels were <0.5 mg/dl.

of the patients had a normal CRP level. For that reason, the prognostic value of CRP was relatively clear for advanced disease.

In conclusion, we verified the results of the Austrian studies, and revealed the prognostic value of NLR and CRP in a large PC cohort. We also found that the cutoff value of 2.0 for NLR clearly demonstrated prognostic value in potentially resectable disease, whereas CRP was a useful prognostic factor in patients who are not good candidates for curative resection. Further investigations to clarify the optimal NLR and CRP cutoff levels are warranted.

Conflict of interest statement

None declared.

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