Combined pretreatment serum CA19-9 and neutrophil-to-lymphocyte ratio as a potential prognostic factor in metastatic pancreatic cancer patients

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Abstract
The aim of this study was to explore the role of combined pretreatment serum carbohydrate antigen 19-9 (CA19-9) and neutrophil-to-lymphocyte ratio (NLR) as potential prognostic factors in metastatic pancreatic cancer patients.

We investigated pretreatment serum CA19-9 and NLR in 59 metastatic pancreatic cancer patients, determined the patients’ thresholds by receiver operating characteristic curve analysis, and assessed their prognostic values by Kaplan–Meier curve and Cox regression models.

Results of multivariate analysis showed high CA19-9, high NLR, and high score (the scoring system of CA19-9 and NLR) were significantly correlated with overall survival. Area under the curve of the scoring system was higher than that of CA19-9 or NLR. Combined pretreatment serum CA19-9 and NLR is a better prognostic biomarker of metastatic pancreatic cancer patients than CA19-9 or NLR alone.

Abbreviations: AUC = area under the curve, CA19-9 = carbohydrate antigen 19-9, CI = confidence interval, NI = not included into multivariate analysis, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, ROC = receiver operating characteristic.

Keywords: CA19-9, metastatic pancreatic cancer, neutrophil-to-lymphocyte ratio, prognostic factor

1. Introduction
Pancreatic cancer is an aggressive cancer with a 5-year survival rate of <7%.[1] It is the seventh leading cause of cancer death worldwide.[2] Around 80% to 85% of diagnosed patients present with locally advanced or metastatic disease, and <20% of patients can proceed with radical resection.[3] The carbohydrate antigen 19-9 (CA19-9) is the most commonly used and best validated serum tumor marker for pancreatic cancer diagnosis in symptomatic patients and for monitoring therapy in patients with pancreatic adenocarcinoma.[4] Several previous studies reported the relationship between the CA19-9 and survival.[5–7] The link between inflammation and cancer was first exploited by Virchow in 1863.[8] Several systemic inflammatory response markers have been investigated to predict survival in various cancers, such as C-reactive protein,[9] neutrophil-to-lymphocyte ratio (NLR),[10] and platelet-to-lymphocyte ratio.[11] NLR has been reported to be associated with the prognosis in patients with pancreatic cancer.[12] It is increasingly recognized that survival of cancer patients was determined not only by tumor characteristics but also by systemic inflammatory response of the host.[13] There have been no studies till date that have reported the prognostic role of combined detection of CA19-9 and NLR in metastatic pancreatic cancer patients and compared the combination with CA19-9 or NLR alone. Hence, the present study analyzes the prognostic utility of CA19-9 or NLR alone in metastatic pancreatic cancer patients. Further, this study determines the prediction ability of combination CA19-9 and NLR in metastatic pancreatic cancer patients.

2. Patients and methods
This retrospective analysis included 59 metastatic pancreatic cancer patients who were treated at Fujian Medical University Union Hospital between 2010 and 2015. The medical records collected in this study were: age, gender, neutrophil count, lymphocyte count, the primary pancreatic tumor location, site of metastasis, levels of CA19-9, type of treatment, follow-up, or death. NLR was calculated as the neutrophil count divided by lymphocyte count. The data was collected within 7 days before treatment. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or the date of last follow-up visit. The study was reviewed and approved by the ethical committee of the Fujian Medical University Union Hospital. According to survival time, patients were divided into subgroups to compare patients who have longer survival time than median OS with patients who had not. The receiver operating characteristic (ROC) curve was generated to evaluate the ideal cut-off values of CA19-9 and NLR for median OS prediction. The Youden index was used to determine the cut-off point. On the basis of each cutoff value, patients were dichotomized into 2
groups. The association between CA19-9 or NLR and other parameters was evaluated by the Pearson \( \chi^2 \) test. Survival data among subgroups classified by each factor were analyzed via the Kaplan–Meier curve, the log-rank test, and Cox proportional hazard model. All variables with significant prognostic value in the univariate analysis were introduced in the final multivariate Cox proportional hazard model. \( P < .05 \) was considered statistically significant. Statistical analysis was performed using the SPSS software 13.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient general characteristics

Fifty-nine patients with metastatic pancreatic cancer diagnosis were enrolled. Of the 59 patients, 40 were males, with a median age of 65 years at diagnosis. Detailed baseline characteristics are listed in Table 1.

3.2. ROC curves of CA19-9 and NLR for median OS

The median CA19-9 was 935U/mL (86–3640U/mL) and the median NLR reached 4.7 (0.9–20.2). ROC curve analysis was used to evaluate cut-off values of CA19-9 and NLR to predict median OS. ROC curve analysis suggested that the cut-off value of 626U/mL for CA19-9 and the cut-off value of 3.75 for NLR were chosen as the optimal value for evaluating median OS (area under the curve [AUC]: 0.744, 95% CI [0.614–0.874], \( P = .001 \), and AUC: 0.764, 95% CI [0.638–0.889], \( P = .001 \), respectively, sensitivity:61.76%, specificity:84.00%, Fig. 1). Furthermore, the scoring system was applied by combining CA19-9 and NLR levels: score 0 was defined as CA19-9 < 626U/mL and NLR < 3.75; score 1 was defined as “CA19-9 ≥ 626U/mL with NLR < 3.75” or “NLR ≥ 3.75 with CA19-9 < 626U/mL”; and score 2 was defined as CA19-9 ≥ 626U/mL and NLR ≥ 3.75.

3.3. Correlations of CA19-9 and NLR with characteristics parameters

Correlations of CA19-9 and NLR with various characteristics parameters including age, gender, tumor location, and site of metastasis were analyzed. As shown in Table 2, there was no

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**Table 1**

| Characteristics | Values/Counts |
|-----------------|--------------|
| Age, years, median (range) | 65 (42–82) |
| Gender (male/female) | 40/19 |
| Tumor location (head/body/tail) | 36/13/10 |
| Metastatic sites (liver/other) | 36/23 |
| Serum CA19-9, U/mL, median (range) | 935 (86–3640) |
| NLR, median (range) | 4.7 (0.9–20.2) |
| Treatment (chemotherapy/other) | 23/36 |
| Survival time, months, median (range) | 4.5 (1–10) |

CA19-9 = carbohydrate antigen 19-9, NLR = neutrophil-to-lymphocyte ratio.

**Table 2**

| Variables | Sum | <626 | \( \geq 626 \) | \( P \) value | \( <3.75 \) | \( \geq 3.75 \) | \( P \) value |
|-----------|-----|------|-------------|-------------|------------|-------------|-------------|
| Age, years | 28 | 14 | 14 | .26 | 13 | 15 | .549 |
| <65 | 31 | 11 | 20 | .248 | 12 | 19 | .248 |
| \( \geq 65 \) | 40 | 19 | 21 | .333 | 19 | 21 | .682 |
| Gender | 19 | 6 | 13 | .687 | 6 | 13 | .138 |
| Male | 36 | 18 | 18 | .453 | 16 | 20 | .7 |
| Female | 13 | 4 | 9 | .453 | 6 | 7 | .16 |
| Tumor location | 10 | 3 | 7 | .453 | 3 | 7 | .138 |
| Head | 36 | 16 | 20 | .453 | 18 | 18 | .7 |
| Body | 23 | 9 | 14 | .453 | 7 | 16 | .16 |
| Tail | Site of metastasis | 34 | 13 | 21 | .453 | 12 | 13 | .21 |
| Liver | 25 | – | – | .453 | 12 | 13 | .21 |
| Other | | | | | | | |
| NLR | .453 | – | – | .453 | .453 | .453 |
| CA19-9, U/mL | .453 | – | – | .453 | .453 | .453 |

CA19-9 = carbohydrate antigen 19-9, NLR = neutrophil-to-lymphocyte ratio.
significant correlation observed between CA19-9 or NLR and other parameters.

3.4. Correlations of characteristics parameters with OS

To investigate whether CA19-9, NLR, and other characteristics, parameters are associated with OS, univariate and multivariate Cox proportional models were calculated. The Kaplan–Meier curves for OS reveal that high levels of CA19-9 or NLR are associated with poor prognosis in metastatic pancreatic cancer (\( P = .0036, P < .0001 \), respectively) (Fig. 2A and B). Univariate analysis identified the age of the patients at diagnosis (\( \geq 65 \) vs \(< 65\), \( P = .0457 \)), CA19-9 (\( \geq 626 \) vs \(< 626\), \( P = .0036 \)), NLR (\( \geq 3.75 \) vs \(< 3.75\), \( P < .0001 \)), the high score of scoring system (score 1 vs score 0, \( P = .0077 \), \( P < .0001 \), respectively), and no chemotherapeutic treatment (no chemotherapy vs chemotherapy, \( P = .0012 \)) were significantly associated with worse OS in metastatic pancreatic cancer, whereas gender, tumor location, and site of metastasis were not (Table 3). All available variables significantly associated with survival in univariable analysis were introduced in a multivariate logistic regression. Multivariate analysis reveals that CA19-9 (\( \geq 626 \) vs \(< 626\), \( P = .0077 \)), NLR (\( \geq 3.75 \) vs \( < 3.75\), \( P < .0001 \)), and the scoring system (score 2 vs score 1 vs score 0, \( P < .0001 \)) were independent prognostic factors for OS (Table 3).

3.5. The scoring system of CA19-9 and NLR is a superior prognostic factor

To determine the independent prognostic significance of the scoring system of CA19-9 and NLR in a metastatic pancreatic cancer patient, Cox regression model and Kaplan–Meier method were performed. The univariate Cox regression and the multivariate Cox regression survival analysis showed that the

**Table 3**

| Variables                  | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
| Age, years                 | HR 95% CI P value   | HR 95% CI P value     |
| <65                        | 1 (referent)        | 1 (referent)          |
| \( \geq 65 \)              | 1.812 1.011–3.247   | 1.388 0.784–2.457     |
| Gender                     | 1 (referent)        | 1 (referent)          |
| Male                       | 1.714 0.8879–3.309  | 1.388 0.784–2.457     |
| Female                     | 0.8797 0.4011–1.555 | 0.972 0.495–1.953     |
| Tumor location             | 1 (referent)        | 1 (referent)          |
| Head                       | 0.7897 0.4011–1.555 | 0.972 0.495–1.953     |
| Body                       | 0.7825 0.3752–1.632 | 0.972 0.495–1.953     |
| Tail                       | 0.7825 0.3752–1.632 | 0.972 0.495–1.953     |
| Site of metastasis         | 1 (referent)        | 1 (referent)          |
| Liver                      | 1.344 0.7411–2.437  | 1.344 0.7411–2.437    |
| Other                      | 1 (referent)        | 1 (referent)          |
| CA19-9, U/mL \( \leq 626 \)| 1 (referent)        | 1 (referent)          |
| \( \geq 626 \)             | 2.364 1.325–4.218   | 2.22 1.240–3.976      |
| NLR \( \leq 3.75 \)        | 1 (referent)        | 1 (referent)          |
| \( \geq 3.75 \)            | 4.214 2.265–7.838   | 3.698 2.044–6.692     |
| Scoring system             | 1 (referent)        | 1 (referent)          |
| 0                          | 2.762 1.309–5.827   | 2.662 1.382–4.471     |
| 1                          | 7.296 3.051–17.40   | 7.296 3.051–17.40     |
| 2                          | 7.296 3.051–17.40   | 7.296 3.051–17.40     |
| Treatment                  | 1 (referent)        | 1 (referent)          |
| Chemotherapy               | 2.61 1.462–4.660    | 1.586 0.900–2.784     |
| No chemotherapy            | 2.61 1.462–4.660    | 1.586 0.900–2.784     |

CA19-9 = carbohydrate antigen 19-9, CI = confidence interval, HR = hazard ratio, NI = not included into multivariate analysis, NLR = neutrophil-to-lymphocyte ratio.
The result of ROC analysis showed that NLR was a better prognostic biomarker of metastatic pancreatic cancer patients than CA19-9 or NLR alone. Further studies are needed to validate the result.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
[2] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[3] Vincent A, Herman J, Schulick R, et al. Pancreatic cancer. Lancet 2013;381:1261–72.
[4] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet (London, England) 2001;357:539–45.
[5] Zou B, Liu J, Wang ZM, et al. C-reactive protein, interleukin 6 and lung cancer risk: a meta-analysis. PLoS One 2012;7:e43075.
[6] Tang X, Du P, Yang Y. The clinical use of neutrophil–lymphocyte ratio in bladder cancer patients: a systematic review and meta-analysis. Int J Clin Oncol 2017;22:817–25.
[7] Zhao Y, Si G, Zhu F, et al. Prognostic role of platelet to lymphocyte ratio in hepatocellular carcinoma: a systematic review and meta-analysis. Oncotarget 2017;8:22854–62.
[8] Picciucci M, Stigliano S, Archibugi L, et al. The neutrophil-to-lymphocyte ratio at diagnosis is significantly associated with survival in metastatic pancreatic cancer patients. Int J Mol Sci 2017;18:730.
[9] Carruthers R, Tho LM, Brown J, et al. Systemic inflammatory response is a predictor of outcome in patients undergoing preoperative chemoradiation for locally advanced rectal cancer. Colorectal Dis 2012;14:e701–7.
[10] Chen Y, Shao Z, Chen W, et al. A varying coefficient Cox model for the effect of CA19-9 kinetics on overall survival in patients with advanced pancreatic cancer. Oncotarget 2017;8:29925–34.
[11] Asaoka T, Miyamoto A, Maeda S, et al. Prognostic impact of preoperative NLR and CA19-9 in pancreatic cancer. Pancreatology 2016;16:434–40.
[12] Wangane B, Orani S, Sakamoto T, et al. Prognostic indicators based on inflammatory and nutritional factors after pancreaticoduodenectomy for pancreatic cancer. Surg Today 2016;46:1258–67.
[13] Xiang JF, Wang WQ, Liu L, et al. Mutant p53 determines pancreatic cancer cell poor prognosis to pancreatectomy through upregulation of cavin-1 in patients with preoperative serum CA19-9 >100 U/mL. Sci Rep 2016;6:19222.
[14] Kim YJ, Koh HK, Chie EK, et al. Change in carbohydrate antigen 19-9 levels as a prognostic marker of overall survival in locally advanced pancreatic cancer treated with concurrent chemoradiotherapy. Int J Clin Oncol 2017;22:1069–75.
[15] Imaoka H, Shimizu Y, Senda Y, et al. Post-adjuvant chemotherapy CA19-9 levels predict prognosis in patients with pancreatic ductal adenocarcinoma: A retrospective cohort study. Pancreatology 2016;16:658–64.
[16] Gu YL, Lan C, Pei H, et al. Applicable value of serum CA19-9, CEA, CA125 and CA242 in diagnosis and prognosis for patients with pancreatic cancer treated by concurrent chemoradiotherapy. Asian Pac J Cancer Prev 2015;16:6569–73.
[21] Nishio K, Kimura K, Amano R, et al. Preoperative predictors for early recurrence of resectable pancreatic cancer. World J Surg Oncol 2017;15:16.
[22] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
[23] Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Brit J Cancer 2013;109:416–21.
[24] Inoue D, Ozaka M, Matsuyama M, et al. 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. Jap J Clin Oncol 2015;45:61–6.
[25] Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev 2017;58:1–3.