Predictive Value of Albumin and Neutrophil Combined Prognostic Grade in Advanced Gastric Cancer Patients Treated With anti-PD-1 Therapy

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Research

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Abstract

Background The application of immunotherapy is gradually increasing in advanced gastric cancer (AGC), but only some patients could benefit from it. Validated biomarkers can screen out the beneficiaries. The objective of this research is to explore the predictive value of albumin and neutrophil combined prognostic grade (ANPG) in AGC patients receiving immunotherapy.

Methods A total number of 268 AGC patients were included. The cut-off value of albumin was 38 g/L obtained by the median value, and neutrophil was 4.16 g/L estimated by the average value. The high levels of albumin (≥38 g/L) and neutrophil (≥4.16 g/L) were considered to be two risk factors for ANPG. Based on these two risk factors, patients were categorized into 3 groups the risk factor number for the "good" group was 0, for the "intermediate" group was 1, and for the "poor" group was 2.

Results Patients with the good ANPG was related to longer progression free survival (PFS) and overall survival (OS), compared to those with the intermediate and the poor ANPG (5.6 months vs 5.3 months vs 3.4 months, 17.8 months vs 11.8 months vs 8.2 months). The poor group was independently correlated with an over 1.9 times risk of disease progression (HR=1.901; 95% CI, 1.314-2.750; P=0.001) and an over 2 times risk of death (HR=2.003; 95% CI, 1.306-3.072; P=0.001) than the good group. The intermediate group was independently correlated with an over 1.3 times risk of disease progression (HR=1.385; 95% CI, 1.004-1.911; P=0.048) and an over 1.4 times risk of death (HR=1.484; 95% CI, 1.046-2.106; P=0.027) than the good group.

Conclusion Our study verifies, for the first time, that ANPG is an independent factor affecting survival of AGC patients receiving immunotherapy. Patients with the good ANPG could benefit from immunotherapy.

1. Introduction

Gastric cancer (GC) is a clinically aggressive gastrointestinal tumors around the world[1]. The incidence rate of GC ranks fifth globally and second domestically in China[1]. The progress of GC treatment is relatively slow, and the traditional chemotherapy, such as surgery, chemotherapy, and targeted therapy are limited. The emergence of immunotherapy brings new option for GC, but its application in GC is difficult. People have tried both back line and front line, as well as single drug and combinations. The ATTRACTION-2 study confirms the efficacy of nivolumab for the back line of GC[2,3]. The results of the KEYNOTE-061 study were negative, and pembrolizumab failed in the second-line challenge chemotherapy[4–6]. The CheckMate 649 study explored that the nivolumab-based first-line immunotherapy was suitable for advanced GC (AGC)[7]. Moehler M et al. found that patients treated with combination of nivolumab and chemotherapy showed improved overall survival (OS) benefits, regardless of the expression status of programmed death ligand-1 (*PD-L1*)[8]. The first result of the KEYNOTE-811 study showed that the combination of pembrolizumab, trastuzumab, and chemotherapy for *HER2*-positive metastatic gastric or gastroesophageal junction cancer [9]. However, the current evaluation of biomarkers for immunotherapy is limited, there is a lack of effective biomarker to be used as a prognostic

factor for AGC patients treated with immune checkpoint inhibitors (ICIs)[10]. In recent years, the expression of *PD-L1* and microsatellite steady-state (MSI) in AGC patients can effectively assess the efficacy of immunotherapy[10,11]. Peripheral blood inflammatory complex index such as lung immune prognostic index (LIPI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and hemoglobin (Hb) levels had demonstrated a convenient and promising prognostic biomarker for GC[12–16]. However, the highly heterogeneous characteristics of GC may limit the accuracy of a single biomarker for screening immunotherapy benefiting populations. In contrast, the combination of multiple indicators can provide more targeted information for the detection of potential immune benefit subgroups. Albumin and neutrophil combined prognostic grade (ANPG) was a composite biomarker of neutrophil and albumin[17]. The high levels of albumin (≥42.55 g/L) and neutrophil (≥2.895 g/L) were considered to be two risk factors for ANPG. Based on these two risk factors, patients were categorized into 3 groups: the risk factor number for the "good" group was 0, for the "intermediate" group was 1, and for the "poor" group was 2[17]. Sun H et al. found that patients with the good ANPG was independently associated with better prognosis for non-small cell lung cancer (NSCLC) patients[17]. However, there is no research on ANPG in immunotherapy of patients with tumor. Thus, we carried out the present study to explore the clinical value of ANPG in predicting prognostic outcomes of AGC patients following ICIs treatment.

2. Materials And Methods

2.1 Study population All patients involved were diagnosed with GC at stage IV and received ICIs treatment in the Senior Department of Oncology, Chinese PLA General Hospital, from December 2014 to May 2021. We set the inclusion criteria as following: 1)patients detected with measurable lesions; 2) patients conducted blood routine and blood biochemistry tests within one week before ICIs administration; 3) patients continuously received at least two rounds of ICIs treatment. Patients failing to provide imaging data for comparing the efficacy of ICIs before and after treatment were excluded. Clinical parameters of patients from their medical records were collected, including smoking history, smoking exposure, sex, age, tumor type, the statu of HER-2 expression, the statu of liver metastasis, response to line before immunotherapy, the statu of pleural fluid, the statu of ascites, the number of metastatic sites, lines of treatment with ICIs, ICIs agent, immunotherapy scheme, and eastern cooperative oncology group performance status scores (ECOG PS). Meanwhile, we analyzed their blood routine parameters 7 days before implementing immunotherapy to obtain albumin and neutrophil values.

2.2 Treatment regimens Five treatment methods were used in this study, including: ICIs monotherapy, ICIs combined with chemotherapy, ICIs combined with anti-angiogenic therapy, ICIs combined with DNA-derived humanized monoclonal antibodies (trastuzumab) and chemotherapy, and CIs combined with chemotherapy and anti-angiogenic therapy. The types and doses of ICIs were as follows: 1) sintilimab was injected intravenously 200 mg once every 3 weeks; 2) toripalimab was injected intravenously 240 mg once every 3 weeks; 3) the recommended dose of pembrolizumab injection for intravenous infusion was a dose of 3 mg/kg, administered once every 3 weeks; 4) the recommended dose of nivolumab injection for intravenous infusion was a dose of 2 mg/kg, administered once every 2 weeks. The first imaging

evaluation of nivolumab was carried out 2-4 weeks after the 3rd intravenous injection, but, the evaluation of toripalimab, sintilimab, and pembrolizumab were carried out 3-5 weeks after the 2rd intravenous injection. The course of trastuzumab was 3 weeks. For the first course, the dose was 8 mg/kg, applied by intravenous injection for 90 minutes. Starting from the 2rd course, the dose was lowered to 6 mg/kg. And for the infusion time, if the patients tolerate trastuzumab well in the first course. Anti-angiogenic drugs involve apatinib (850 mg, orally administrated 30 min after a meal, once a day), and bevacizumab (5 mg/kg body weight, once every two weeks; or 7.5 mg/kg body weight, once every 3 weeks). The chemotherapy regimens include 1) XELOX regimen: capecitabine (1000mg/m²) was used 2 times a day orally after breakfast and dinner for 14 consecutive days with 7 days of rest as a treatment cycle. oxaliplatin (130mg/m²) was added at the first day of each cycle by intravenous injection; 2) SOX regimen: tiggio: (40-60mg) was used 2 times a day orally after breakfast and dinner for 14 consecutive days with 7 days of rest as a treatment cycle. oxaliplatin (130mg/m²) was added at the first day of each cycle by intravenous injection; 3) DCF regimen: docetaxel (75mg/m²), cisplatin (75mg/m²), and fluorouracil (750mg/m²) were applied by intravenous injection. On the first day of every course, each course lasted 21 days. 4) The combined regimen of irinotecan and oxaliplatin: irinotecan (180 mg/m²) and oxaliplatin (130mg/m²) were applied by intravenous injection. On the first day of every course, each course lasted 14 days. 5) The combined regimen of irinotecan and raltitrexed: irinotecan (180 mg/m²) and raltitrexed (3 mg/m²) were applied by intravenous injection. On the first day of every course, each course lasted 14 days. 6) others. The choice of the above regimens was based on the patient's pathological stage, general health conditions.

2.3 Assessment For efficacy evaluation, the disease control rate(DCR)and the overall response rate (ORR) is termed as the percentage of patients with complete response (CR), partial response (PR) and stable disease (SD) and the percentage of patients with CR and PR, respectively. For prognosis analysis, OS and progression free survival (PFS) are the time from the begining of immunotherapy to death and the time between the onset of ICIs and the progression or death of the tumor, respectively.

2.4 Neutrophil, albumin, and ANPG We analyzed the value of neutrophil, and albumin 7 days before implementing immunotherapy. The cut-off value of albumin was estimated by the median value and neutrophil was obtained by the average value. The high levels of albumin (≥ the median value) and neutrophil (≥ the average value) were considered to be two risk factors for ANPG. Based on these two risk factors, patients were categorized into 3 groups: the risk factor number for the "good" group was 0, for the "intermediate" group was 1, and for the "poor" group was 2.

2.5 Statistical analysis SPSS 26.0 software was used to perform all statistical analysis. Datas were summarized as the minimum–maximum range and median for non-normally distributed continuous variables. Datas were reported as percentages and counts for categorical variables. $\chi 2$ or Fisher exact test was carried out to evaluate the relationship between clinical response and ANPG groups of AGC patients. The survival curve was depicted by Kaplan–Meier analysis. Logistic regression models and Cox proportional hazard were applied to assess the prognostic values of ANPG groups for DCR, and survival, respectively. Values of P less than 0.05 ($p<0.05$) were considered statistically significant.

3. Results

3.1 Baseline characteristics A total of 268 AGC patients receiving ICIs were retrospectively reviewed in the study. The clinical feature of patients were provided below (Table 1). The cut-off value of albumin and neutrophil were 38 g/L and 4.16 g/L, respectilvely. After grouping, the numbers of patients with the good ANPG, with the intermediate ANPG, and with the poor ANPG were ninety five, one hundred and eighteen, and fifty-five. The median age of patients with the good ANPG, the poor ANPG,and the poor ANPG were 56-year-old, 60-year-old, and 59-year-old, respectively. Patients were predominantly male (74.3%), no history of smoking (62.3%), short history of smoking exposure (smoking exposure history is less than or equal to 30 years in 82.1% of cases), ECOG PS of 0-1 ((94%), the tumor location of Body/Fundus (41%), no hepatic metastasis (55.6%), negative expression of *HER-2* (66%), no pleural fluid (92.9%), no ascites (75.4%) and had fewer organ metastasis (the number of metastatic sites of 0-2 in 75.4% of cases)

3.2 Treatment characteristics Of 268 patients, 175 (65.3%) patients had previously progressed before using ICIs;88 (32.8%) patients received nivolumab, 36 (13.4%) patients were treated with pembrolizumab and 144 (53.7%) patients received other immunotherapy drugs; 143 (53.4%) patients used the 1st line ICIs ; and 173 (64.6%) patients were recieving the combinated plan of immunotherapy and chemotherapy (Table 1).

3.3 ANPG for response to ICIs The optimal efficacy of all AGC patients was evaluated in the study, and the results were as follows: 111 (41.4%) patients had progressive disease (PD), 4 (1.5%) patients had CR, 78 (29.1%) patients had PR, and 75 (28%) patients had SD. The ORR was 30.6% and DCR was 58.6% (Table 2). Patients with poor, intermediate, and good ANPG did not show clear difference in DCR (50.9% vs 55.9% vs 66.3%, p=0.134), or in ORR (27.3% vs 34.7% vs 27.4%; P=0.425) (Table 2).

3.4 ANPG for PFS of AGC patients Among 268 AGC patients, 220 (82.1%) patients had tumor progression within the last follow-up date of July 1, 2021. Patients in good ANPG group were closely related to longer PFS, compared to those in the intermediate and poor ANPG group (5.6 months vs 5.3 months vs 3.4 months; P=0.002) (Figure 1a and Table 3). Univariate and multivariate analyses of factors associated with PFS were shown in Table 3. In univariate analysis, patients with a good PS (ECOG PS of 0-1), with no ascites, or with no pleural fluid showed improved OS. Patients did not reach PD before immunotherapy, and those who were treated with ICIs combined with chemotherapy, who were treated with the 1st line ICIs, and who were treated with pembrolizumab were also associated with improved PFS. Multivariate analysis revealed that the poor ANPG and the intermediate ANPG were independently correlated with an over 1.9 times risk of disease progression (HR=1.901; 95% CI, 1.314-2.750; P=0.001) and an over 1.3 times risk of disease progression (HR=1.385; 95% CI, 1.004-1.911; P=0.048) than the good ANPG. Moreover, patients who were treated with ICIs combined with chemotherapy, who were treated with the 1st line ICIs, and who were treated with pembrolizumab were also independently associated with improved PFS. Patients treated with ICIs after 1st line were independently correlated with an over 1.6 times risk of disease progression (HR=1.699; 95% CI,1.244-2.320; P=0.001) than those treated with the 1st line ICIs. Patients treated with nivolumab were independently correlated with an over 1.9 times risk of disease

progression (HR=1.972; 95% CI,1.259-3.089; P=0.003) than those treated with pembrolizumab. Patients treated with ICIs combined without chemotherapy were independently correlated with an over 1.4 times risk of disease progression (HR=1.424; 95% CI,1.034-1.961; P=0.03) than those treated with ICIs combined with chemotherapy.

3.5 ANPG for OS of AGC patients Among 268 AGC patients, 175 (65.3%) patients died within the last follow-up date of July 1, 2021. Patients in the good ANPG group were closely related to longer OS, compared to those in the intermediate and poor ANPG group (17.8 months vs 11.8 months vs 8.2 months; P=0.003) (Figure 1b and Table 3). Univariate and multivariate analyses of factors associated with OS were shown in Table 3. In univariate analysis, In univariate analysis, patients with fewer organ metastases (<3), with a good PS (ECOG PS of 0-1), with no ascites, or with no pleural fluid showed improved OS. Patients did not reach PD before immunotherapy, and those who were treated with ICIs combined with chemotherapy, who were treated with the 1st line ICIs, and who were treated with pembrolizumab were also associated with improved OS. Multivariate analysis revealed that the poor ANPG and the intermediate ANPG were independently correlated with an over 2 times risk of death (HR=2.003; 95% CI, 1.306-3.072; P=0.001) and an over 1.4 times risk of death (HR=1.484; 95% CI, 1.046-2.106; P=0.027) than the good ANPG. Moreover, patients with no pleural fluid and with a good PS (ECOG PS of 0-1) were independently associated with improved OS. Patients who were treated with the 1st line ICIs and who were treated with pembrolizumab were also independently associated with improved OS. Patients with pleural fluid were independently correlated with an over 2.2 times risk of death (HR=2.252; 95% CI, 1.333-3.804; P =0.002) than those without pleural fluid. Patients with a good PS (ECOG PS of 0-1) were independently correlated with an over 1.9 times risk of death (HR=1.996; 95% CI, 1.122-3.552; P =0.019) than those with a poor PS (ECOG PS of ≥2). Patients treated with ICIs after 1st line were independently correlated with an over 1.8 times risk of death (HR=1.817; 95% CI,1.315-2.512; P<0.001) than those treated with the 1st line ICIs. Patients treated with nivolumab were independently correlated with an over 1.5 times risk of death(HR=1.577; 95% CI,1.005-2.476; P=0.048) than those treated with pembrolizumab.

3.6 Association of the ANPG with outcomes in lines of immunotherapy of 1 or a large number of lines of immunotherapy (≥2): Subgroup Analysis Multivariate analysis revealed that patients treated with the 1st line ICIs were independently correlated with improved OS and PFS. Our study then conducted subgroup analysis based on different lines of immunotherapy. Univariate analyses of association of the ANPG with outcomes in lines of immunotherapy of 1 was shown in Table 4. For the 143 patients with the 1st line ICIs, 23 (41.8%) patients were in the poor ANPG group, 63(53.4%) patients were in the intermediate ANPG group, and 39 (41.1%) patients were in the good ANPG group. Pateints of the good ANPG group had improved PFS than the intermediate ANPG group ,and the poor ANPG group (14.6 months vs 8.1 months vs 5.8 months, P=0.021) (Figure2a). The poor ANPG was correlated with an over 2.3 times risk of disease progression (HR=2.328; 95% CI, 1.269-4.272; P=0.006) than the good ANPG. However, patients with good, intermediate, and poor ANPG did not show clear difference in OS (29 months vs 15.8 months vs 12.9 months, P=0.218) (Figure 2b). Univariate analyses of association of the ANPG with outcomes in lines of a large number of lines of immunotherapy (≥2) was shown in Table 5. For 125 patients with ICIs in

subsequent lines, 32(58.2%) patients were in the poor ANPG group, 55(46.6%) patients were in the intermediate ANPG group, and 56(58.9%) patients were in the good group. Pateints of the good ANPG group had improved PFS and OS than the intermediate ANPG group, and the poor ANPG group (3.3 months vs 3.4 months vs 2.2 months, 11.9 months vs 9.1 months vs 3.7 months; P=0.026,P=0.001) (Figure 3a,3b). The poor ANPG was correlated with an over 1.7 times risk of disease progression (HR= 1.773; 95% CI, 1.126-2.791; P=0.013) and an over 2.3 times risk of death (HR=2.371; 95% CI, 1.467-3.834; P=0.006) than the good ANPG. However, patients with intermediate, and good ANPG did not show clear difference in OS and PFS (P=0.148, P=0.790).

3.7 Association of the ANPG with outcomes in ICIs combined with chemotherapy or combined without chemotherapy: Subgroup Analysis Multivariate analysis revealed that patients treated with the ICIs combined with chemotherapy were independently correlated with improved OS and PFS. Our study then conducted subgroup analysis based on different schemes of immunotherapy. Univariate analyses of association of the ANPG with outcomes in ICIs combined with chemotherapy was shown in Table 6. For the 173 patients treated with the ICIs combined with chemotherapy, 32(58.2%) patients were in the poor ANPG group, 82(64.6%) patients were in the intermediate ANPG group, and 59(62.1%) patients were in the good ANPG group. Pateints of the good ANPG group had improved PFS than the intermediate ANPG group ,and the poor ANPG group (6.7 months vs 6 months vs 3.7 months, P=0.049)(Figure 4a). The poor ANPG was correlated with an over 1.6 times risk of disease progression (HR=1.649; 95% CI, 1.027-2.648; P=0.039) and an over 1.8 times risk of death (HR=1.827; 95% CI, 1.058-3.155; P=0.031) than the good ANPG. However, patients with good, intermediate, and poor ANPG did not show clear difference in OS (20.9 months vs 14.9 months vs 8.7 months, P=0.091) (Figure 4b). Univariate analyses of association of the ANPG with outcomes in lines of immunotherapy of 1 shown in Table 7. For 95 patients treated with the ICIs combined without chemotherapy, 23 (41.8%) patients were in the poor ANPG group, 36 (30.5%) patients were in the intermediate ANPG group, and 36 (37.9%) patients were in the good group. Pateints of the good ANPG group had improved PFS and OS than the intermediate ANPG group, and the poor ANPG group (3.2 months vs 2.8 months vs 2.2 months, 12.7 months vs 8.1 months vs 5.4 months; P=0.032,P=0.007) (Figure5a,5b). The poor ANPG was correlated with an over 2.4 times risk of disease progression (HR=2.422; 95% CI, 1.367-4.292; P=0.002) and an over 2.1 times risk of death (HR=2.184; 95% CI, 1.194-3.994; P=0.011) than the good ANPG. However, patients with good and intermediate ANPG did not show clear difference in OS and PFS(P=0.096, P=0.051).

4. Discussion

The status of immunotherapy in the field of GC treatment has an increasing trend worldwide annually[7,18]. Judging from the current clinical trial results, the effect of immune checkpoint inhibitors is very obvious[19].Whereas, immunotherapy drugs are expensive and prone to drug resistance and even super-progress[20,21]. Therefore, looking for predictive indicators is an important problem to be solved urgently that can accurately identify the population with the advantage of immunotherapy to achieve precise immunotherapy as much as possible. However, the current evaluation of biomarkers for

immunotherapy is relatively limited[15]. Peripheral blood inflammatory complex index such as LIPI, NLR, PLR, Hb levels had demonstrated a convenient and promising prognostic biomarker for GC[12–16]. The highly heterogeneous characteristics of GC may limit the accuracy of a single biomarker for screening immunotherapy benefiting populations[22]. In contrast, the combination of multiple indicators can provide more targeted information for the detection of potential immune benefit subgroups. Sun H et al. found that patients with the good ANPG was independently associated with better prognosis for NSCLC patients[17]. ANPG was a composite biomarker of neutrophil and albumin[17]. The high levels of albumin (≥the cut-off value) and neutrophil (≥the cut-off value) were considered to be two risk factors for ANPG. Based on these two risk factors, patients were categorized into 3 groups: the risk factor number for the "good" group was 0, for the "intermediate" group was 1, and for the "poor" group was 2[17]. However, there is no research on ANPG in immunotherapy of patients with tumor. Thus, we carried out the present study to explore the clinical value of ANPG in predicting prognostic outcomes of AGC patients following ICIs treatment. In our study, the cut-off value of albumin was 38 g/L obtained by the median value, and neutrophil was 4.16 g/L estimated by the average value. We found that patients in good ANPG group were independently related to longer PFS and OS, compared to those in the intermediate and poor ANPG group. The prognostic value of ANPG in AGC patients treated with ICIs was consistent with in NSCLC patients of the study of Sun H et al[17]. Moreover, subgroup analysis of our study, based on different lines of immunotherapy, found that ANPG was correlated with PFS but not OS of AGC patients treated with the 1st line ICIs and was correlated with PFS and OS of AGC patients treated with ICIs in subsequent lines. Subgroup analysis of our study, different schemes of immunotherapy, found that ANPG was correlated with PFS but not OS of AGC patients treated with ICIs combined with chemotherapy and was correlated with PFS and OS of AGC patients treated with ICIs combined without chemotherapy. Baicun Hou et al. noticed that patients with a good PS (ECOG PS of 0-1) were also independently associated with PFS and OS for AGC patients treated with ICIs[16]. But, in our study, patients had a good PS (ECOG PS of 0-1) were independently associated with improved OS, but without improved PFS. Baicun Hou et al. noticed that patients treated with combination of immunotherapy and other therapies were associated with improved OS and PFS[16]. Patients receiving ICIs combined without chemotherapy were associated with shorter PFS but not OS in our study. We found patients treated with the 1st line ICIs were independently associated with improved PFS and OS. However, no clear difference of OS and PFS were observed between patients treated with the 1st line ICIs and treated with ICIs after the 1st line in study of Baicun Hou et al.[16]. Baicun Hou et al. found that patients had fewer organ metastases (< 2) and treated with the 1st line ICIs were not independently associated with improved PFS and OS than those had more organ metastases (≥2)[16]. We also found patients had fewer organ metastases (< 3) were not independently associated with improved PFS and OS. Baicun Hou et al. found that the type of ICIs was not an independent factor affecting survival of AGC patients receiving immunotherapy[16]. However, our study found that patients treated with pembrolizumab were independently correlated with improved OS and PFS than those treated with nivolumab. In addition, our study firstly found that patients without pleural fluid were independently correlated with improved OS than those with pleural fluid, but without improved PFS.

However, the mechanism of the correlation between these peripheral blood inflammatory complex index and the tumor prognosis is relatively complicated, and it still needs to be further explored through basic experiments and clinical trials. Some studies have found that this probably due to the tumor-immune microenvironment of patients[23,24]. In addition to direct immune killing effects on tumor cells, these biomarkers are also related to tumor immunostimulatory signals and the activation of effector cells. Neutrophils, one type of the most vital and abundant leukocytes in circulating blood, are the first-line defense to protect host from tissue damage and infections[25]. Neutrophils are derived from bone marrow hematopoietic stem cells and have chemotaxis, phagocytosis and bactericidal effect[26]. The reactive oxygen species released by neutrophils can damage DNA, which is related to the occurrence and development of tumors[27]. Increased number of neutrophils in peripheral blood can promote tumor metastasis and growth by releasing inflammatory mediators[28]. In addition, it can not only enhance the growth of tumor cells under the effect of tumor, its microenvironment reproduction and invasion can promote angiogenesis and mediate tumor immunosuppression[29]. Lymphocyte is an important component of cell for body's immune response function[30]. Elevated neutrophils can inhibit the immune attack ability of lymphocytes[31]. Albumin one type of the most vital biochemical Indicators, is related to nutritional status of patients with cancer[32]. Some studies found that hypoalbuminemia are associated with worse prognosis of patients with GC[33,34]. Some researchers thought if it was associated with other powerful clinical indicators, such as c-reactive protein (CRP), the albumin level as a prognostic indicator would be more convincing[35,36]. Nozoe T et al. found glasgow prognostic score (GPS) which was a composite biomarker of albumin and CRP could be used as an positive prognostic indicator of patients with GC[36]. Zhang J et al. found that a composite biomarker of serum carcinoembryonic antigen (CEA) and fibrinogen/ albumin ratio also could be used as an positive prognostic indicator of patients with GC[37]. Therefore, the higher level of neutrophils and the lower level of tumor patients get, the worse their prognosis will be. ANPG was a composite biomarker of neutrophil and albumin[17]. In other words, patients with good ANPG will have a better prognosis.

This study had some limitations, including a relatively small sample size with a mixed population of GC of cardia, GC of body/fundus, and GC of pylorus, as well as a lack of comparison of the three ANPG groups among the three cancers.

Conclusion

This study demonstrated that a composite biomarker of ANPG is independently correlated with the survival of AGC patients implementing immunotherapy. However, the possibility of using the complex index as an effective and economic prognostic biomarker to selected patients, those who are best suited to receiving ICIs, needs further investigation in a larger prospective study.

Abbreviations

Gastric cancer (GC);advanced GC (AGC);verall survival (OS); programmed death ligand-1 (*PD-L1*); immune checkpoint inhibitors (ICIs); microsatellite steady-state (MSI);lung immune prognostic index (LIPI); neutrophil-lymphocyte ratio (NLR); platelet-lymphocyte ratio (PLR); hemoglobin (Hb); progression free survival (PFS); albumin and neutrophil combined prognostic grade (ANPG); non-small cell lung cancer (NSCLC); eastern cooperative oncology group performance status scores (ECOG PS); disease control rate （DCR); overall response rate (ORR) ; complete response (CR); partial response (PR) ; stable disease (SD) ; progressive disease (PD); c-reactive protein (CRP);glasgow prognostic score (GPS); carcinoembryonic antigen (CEA)

Declarations

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Chinese PLA General Hospital and was conducted according to the principles of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

YP were in charge of writing and analysis. GD and ZK provided the guide and idea. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables

Table 1 General data and clinical feature

Characteristics	No. of patients (%)			
	Overall (n = 268)	the good ANPG (n = 95)	the intermediate ANPG (n = 118)	the poor ANPG (n = 55)
Median age (range), years	59(18-86)	56(27-83)	60(22-86)	59(18-77)
Sex				
Female	69(25.7)	27(28.4)	28(23.7)	14(25.5)
Male	199(74.3)	68(71.6)	90(76.3)	41(74.5)
Smoking history				
Yes	101(37.7)	42(44.2)	37(31.4)	22(40)
No	167(62.3)	53(55.8)	81(68.6)	33(60)
Response to line before immunotherapy				
PD	175(65.3)	70(73.7)	71(60.2)	21(38.2)
Others	93(34.7)	25(26.3)	47(39.8)	34(61.8)
Number of metastatic sites				
≥3	66(24.6)	14(14.7)	33(28)	19(34.5)
<3	202(75.4)	81(85.3)	85(72)	36(65.5)
Pleural fluid				
Present	19(7.1)	5(5.3)	10(8.5)	4(7.3)
Absent	249(92.9)	90(94.7)	108(91.5)	51(92.7)
Liver metastasis				
Present	119(44.4)	35(36.8)	54(45.8)	30(54.5)
Absent	149(55.6)	60(63.2)	64(54.2)	25(45.5)
Ascites				
Present	66(24.6)	27(28.4)	23(19.5)	16(29.1)
Absent	202(75.4)	68(71.6)	95(80.5)	39(70.9)
HER-2				
Present	34(12.7)	10(10.5)	17(14.4)	7(12.7)
Absent	177(66)	65(68.4)	76(64.4)	36(65.5)
Unknown	57(21.3)	20(21.1)	25(21.2)	12(21.3)

Lines of immunotherapy				
≥2	143(53.4)	56(58.9)	55(46.6)	32(58.2)
<2	125(46.6)	39(41.1)	63(53.4)	23(41.8)
Tumor_location				
Cardia	73(27.2)	27(28.4)	28(23.7)	18(27.2)
Body/Fundus	110(41)	39(41.1)	47(39.8)	24(41)
Pylorus	83(31)	28(29.5)	42(35.6)	13(31)
Unknown	2(0.7)	1(1.1)	2(0.8)	0(0)
Smoking exposure				
> 30 packs per year	48(17.9)	17(17.9)	19(16.1)	12(21.8)
≤ 30 packs per year	220(82.1)	78(82.1)	99(83.9)	43(78.2)
ECOG performance status				
≥ 2	16(6)	1(1.1)	6(5.1)	9(16.4)
0-1	252(94)	94(98.9)	112(94.9)	46(83.6)
PD-1 inhibition agent				
Pembrolizumab	36(13.4)	14(14.7)	16(13.6)	6(10.9)
Nivolumab	88(32.8)	29(30.5)	35(29.7)	24(43.6)
Other	144(53.7)	52(54.7)	67(56.8)	25(45.5)
ICIs combined with chemotherapy				
Yes	173(64.6)	59(62.1)	82(64.6)	32(58.2)
No	95(35.4)	36(37.9)	36(30.5)	23(41.8)

Table 2 Relationship between ANPG groups and response to anti-PD-1 treatment

Best Overall Respons	No. of Patients (%)				P value
	Overall n =110	the good ANPG n =38	the intermediate ANPG n = 72	the poor ANPG n = 72	
CR	4（1.5）	1（1.1）	2（1.7）	1（1.8）	0.579
PR	78（29.1）	25(26.3)	39（33.1)	14(25.5)	0.448
SD	75（28）	37(38.9)	25(21.2)	13(23.6)	0.012
PD	111 （41.4）	32(33.7)	52(44.1)	27(49.1)	0.134
Objective response	82(30.6)	26(27.4)	41（34.7）	15（27.3）	0.425
Disease control rate	157 （58.6）	63(66.3)	66（55.9）	28（50.9）	0.134

Table 3 Univariate and multivariate analyses of factors associated with overall survival and progression-free survival

OS					
ECOG performance status, No.					
0-1	13.1	1 [Reference]		1 [Reference]	
≥ 2	2	4.466(2.647-7.534)	<0.001*	1.996(1.122-3.552)	0.019
Lines of immunotherapy					
<2	20.9	1 [Reference]		1 [Reference]	
≥2	9.1	2.106(1.543-2.874)	<0.001*	1.817（1.315-2.512）	<0.001*
Ascites					
Absent	13.1	1 [Reference]		1 [Reference]	
Present	11.1	1.443(1.039-2.003)	0.029*	1.174（0.821-1.677）	0.380
Pleural fluid					
Absent	12.8	1 [Reference]		1 [Reference]	
Present	6.0	2.249(1.340-3.776)	0.002*	2.252(1.333-3.804）	0.002
Number of metastatic sites					
<3	14	1 [Reference]		1 [Reference]	
≥3	9	1.556(1.122-2.157)	0.008*	1.275(0.901-1.806)	0.170
Response to line before immunotherapy					
Others	18.3	1 [Reference]		1 [Reference]	
PD	11.1	1.543(1.112-2.143)	0.001*	1.065(0.724-1.565)	0.750
ICIs combined with chemotherapy					
Yes	15	1 [Reference]		1 [Reference]	
No	9.3	1.518(1.121-2.055)	0.007	1.151(0.810-1.635)	0.434
PD-1 inhibition agent					
Pembrolizumab	12.7	1 [Reference]		1 [Reference]	
Nivolumab	5.7	1.659(1.062-2.592)	0.026*	1.577（1.005-2.476）	0.048
Others	19.7		0.027*		0.059

		0.603(0.385-0.945)		0.639（0.402-1.017）	
ANPG					
The good	17.8	1 [Reference]		1 [Reference]	
The intermediate	11.8	1.333（0.943-1.885）	0.103	1.484（1.046-2.106）	0.027
The poor	8.2	1.993（1.330-2.986）	0.001	2.003（1.306-3.072）	0.001
Patient Characteristics	survival(months）	Univariate Analysis HR （95%CI）	P	Multivariate Analysis HR （95%CI）	P
PFS					
ECOG performance status, No.					
0-1	5.3	1 [Reference]		1 [Reference]	
≥ 2	1.9	2.526(1.511-4.222)	<0.001*	1.063(0.601-1.878)	0.835
Lines of immunotherapy					
<2	8.1	1 [Reference]		1 [Reference]	
≥2	3.1	2.083(1.586-2.737)	<0.001*	1.699(1.244-2.320)	0.001
Ascites					
Absent	5.2	1 [Reference]		1 [Reference]	
Present	3.6	1.491(1.103-2.015)	0.009*	1.381（0.989-1.928）	0.058
Pleural fluid					
Absent	5.3	1 [Reference]		1 [Reference]	
Present	2.5	2.029(1.242-3.317)	0.005*	1.6050.936-2.751）	0.085
Response to line before immunotherapy					
Others	5.8	1 [Reference]		1 [Reference]	
PD	4.2	1.330(1.000-1.770)	0.048*	0.883(0.628-1.241)	0.474
ICIs combined with chemotherapy					
Yes	5.8	1 [Reference]		1 [Reference]	
No	3.0	1.588(1.212-2.081)	0.001	1.424（1.034-1.961）	0.030

PD-1 inhibition agent					
Pembrolizumab	6.9	1 [Reference]		1 [Reference]	
Nivolumab	2.4	1.835(1.193-2.822)	0.006*	1.972（1.259-3.089）	0.003
Others	5.8	0.980(0.646-1.485)	0.992	1.073（0.700-1.646）	0.747
ANPG					
The good	5.6	1 [Reference]	0.003	1 [Reference]	
The intermediate	5.3	1.128（0.829-1.534）	0.444	1.385（1.004-1.911）	0.048
The poor	3.4	1.857（1.295-2.662）	0.001	1.901（1.314-2.750）	0.001

Table 4 Univariate analyses of ANGP associated with overall survival and progression-free survival of AGC patients treated with 1st line ICIs

ANGP classification	Patients treated with the 1st line ICIs					
	OS (months)			PFS (months)		
	Median	HR(95%CI)	P value	Median	HR(95%CI)	p value
The good	29	1 [Reference]		14.6	1 [Reference]	
The Intermediate	15.8	1.639 (0.906-2.967)	0.103	8.1	1.484 (0.892-2.469)	0.129
The poor	12.9	1.682 (0.793-3.566)	0.175	5.8	2.328 (1.269-4.272)	0.006
P value	0.218			0.021		

Table 5 Univariate analyses of ANGP associated with overall survival and progression-free survival of AGC patients treated with ICIs in subsequent lines

ANGP classification	Patients treated with ICIs in subsequent lines					
	OS (months)			PFS (months)		
	Median	HR(95%CI)	P value	Median	HR(95%CI)	p value
The good	11.9	1 [Reference]		3.3	1 [Reference]	
The Intermediate	9.1	1.379 (0.892-2.133)	0.148	3.4	1.056(0.708-1.575)	0.790
The poor	3.7	2.371(1.467-3.834)	<0.001	2.2	1.773 (1.126-2.791)	0.013
P value	0.001			0.026		

Table 6 Univariate analyses of ANGP associated with overall survival and progression-free survival of AGC patients treated with ICIs combined with chemotherapy.

ANGP classification	Patients treated with ICIs combined with chemotherapy					
	OS (months)			PFS (months)		
	Median	HR(95%CI)	P value	Median	HR(95%CI)	p value
The good	20.9	1 [Reference]		6.7	1 [Reference]	
The Intermediate	14.9	1.255 (0.801-1.965)	0.321	6	0.955 (0.664-1.471)	0.955
The poor	8.7	1.827 (1.058-3.155)	0.031	3.7	1.649(1.027-2.648)	0.039
P value	0.091			0.049		

Table 7 Univariate analyses of ANGP associated with overall survival and progression-free survival of AGC patients treated with ICIs combined without chemotherapy.

ANGP classification	Patients treated with ICIs combined without chemotherapy					
	OS (months)			PFS (months)		
	Median	HR(95%CI)	P value	Median	HR(95%CI)	p value
The good	12.7	1 [Reference]		3.2	1 [Reference]	
The Intermediate	8.1	1.589 (0.922-2.741)	0.096	2.8	1.650 (0.998-2.729)	0.051
The poor	5.4	2.184 (1.194-3.994)	0.011	2.2	2.422(1.367-4.292)	0.002
P value	0.032			0.007		

Figures

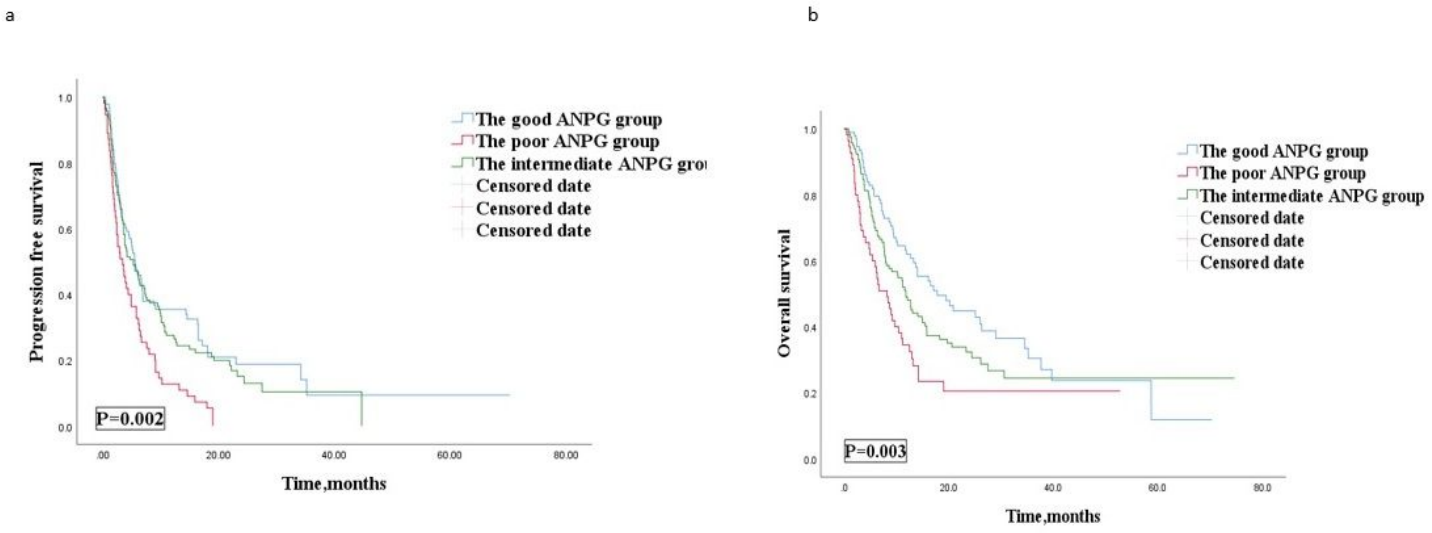

Figure 1

progression-free survival (PFS) (a) and Overall survival (OS) (b) according to the good ANPG, the intermediate ANPG and the poor ANPG groups of patients with AGC patients.

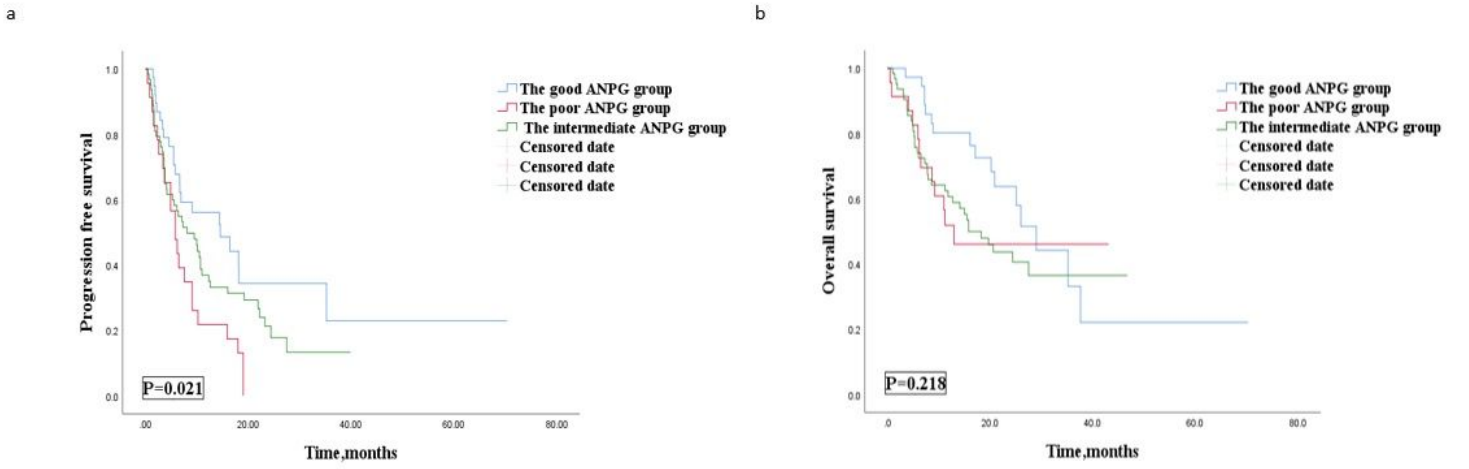

Figure 2

PFS (a)and (b) OS of the 1st line of patients with AGC, receiving PD-1 inhibitor cohort.

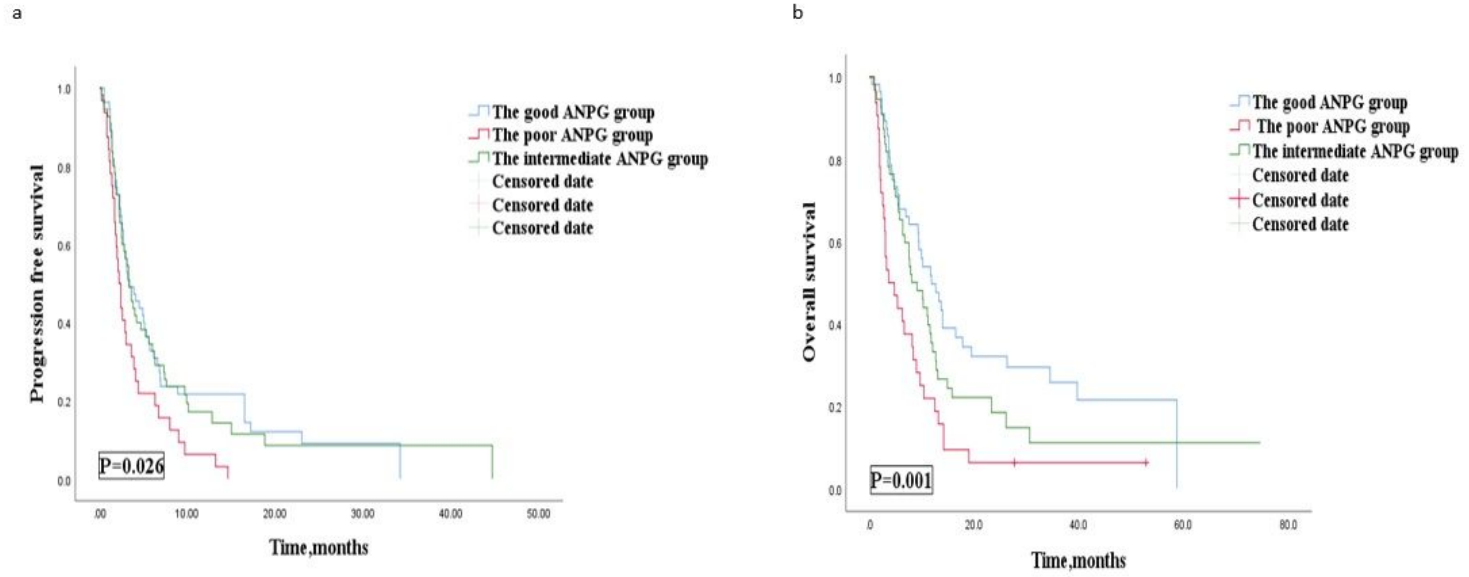

Figure 3

PFS (a)and (b) OS of the the multi-line of patients with AGC, receiving PD-1 inhibitor cohort.

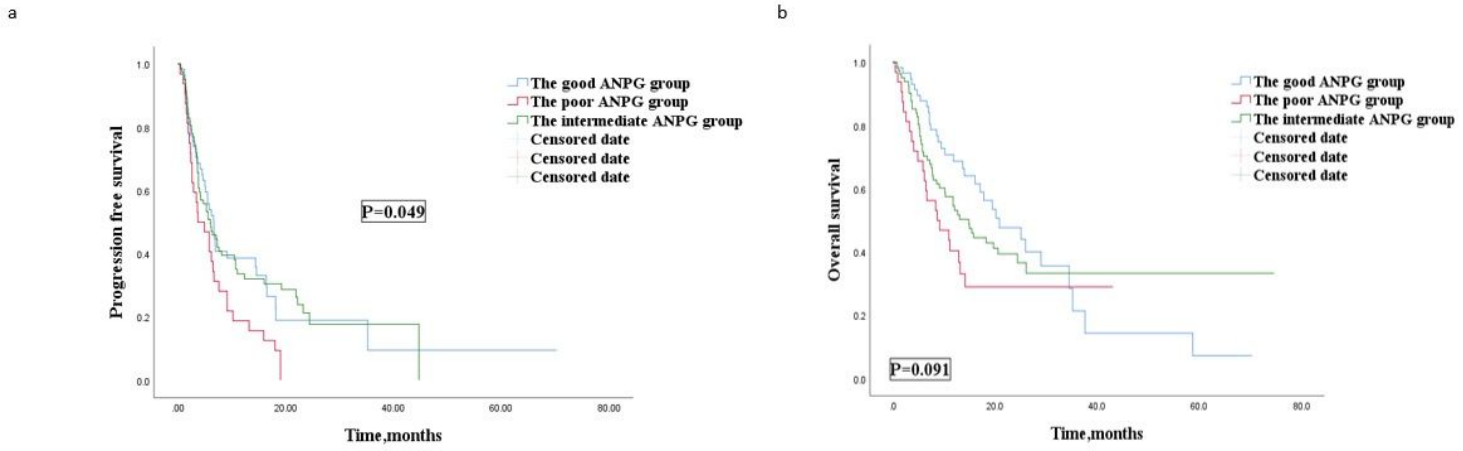

Figure 4

PFS (a)and (b) OS of AGC patients treated with ICIs combined with chemotherapy, receiving PD-1 inhibitor cohort.

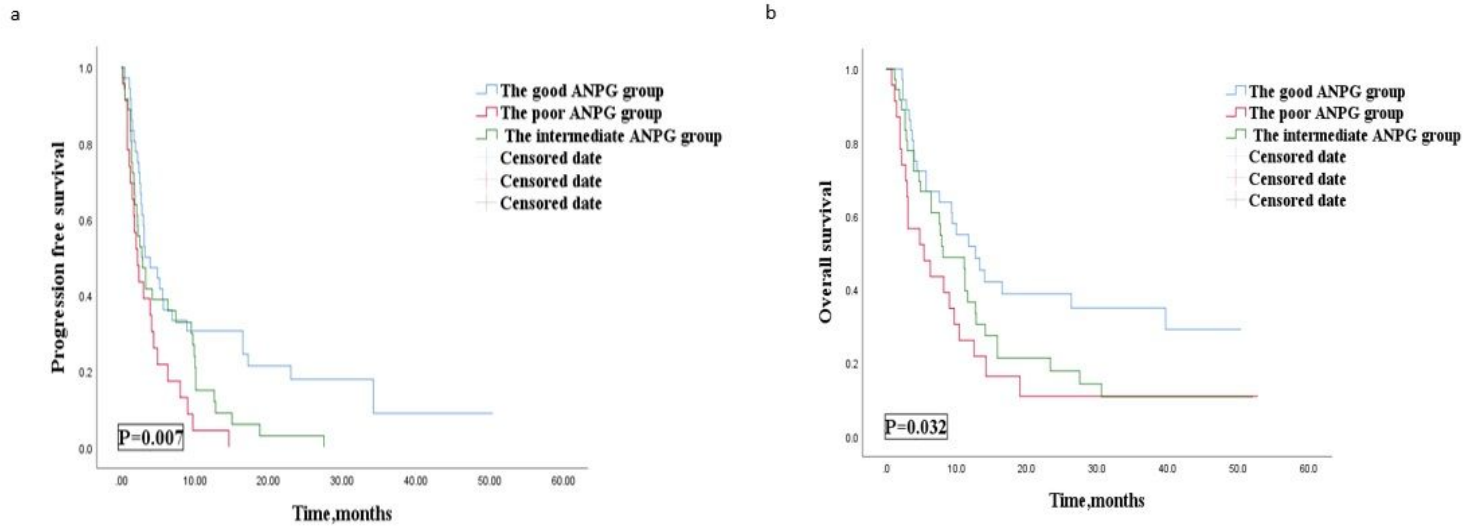

Figure 5

PFS (a) and (b) OS of AGC patients treated with ICIs combined without chemotherapy, receiving PD-1 inhibitor cohort.