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Is There a Novel Prognostic Parameter for Well-Differentiated Neuroendocrine Tumours?

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ABSTRACT

Background: Neuroendocrine tumours (NETs) are a heterogeneous group of tumours. There are no well-established prognostic factors for accurately predicting survival of patients with well-differentiated NETs. Prognostic value of inflammatory markers was evaluated in some solid tumours previously. However, it was not well documented in orphan tumours like well-differentiated NETs. We aimed to find out a novel and easy-accessible prognostic parameter by using hemogram & biochemical parameters in patients with well-differentiated NETs.

Patients and Methods: 132 patients with well-differentiated NETs were analyzed, retrospectively. Patients were subgrouped into two groups with respect to the cut-off value that was determined by ROC analysis. Survival analysis was performed by using the Kaplan-Meier method with the Long-rank test. $p<0.05$ was considered statistically significant.

Results: The cut-off value was defined as 47.94 for AlbXHb. High-risk (AlbXHb < 47.94) group had significantly increased risk of death (HR:5.16, 95%CI 1.45-18.38 p=0.011). AlbXHb was a significant prognostic factor for OS in univariate analyses (HR=0.925 95% CI 0.878-0.974, p=0.003).

Conclusion: We demonstrated that AlbXHb might be a novel prognostic factor for well-differentiated NETs, but it needs further evaluation by randomized clinical trials. We believe that this novel parameter has feasible accuracy for predicting disease outcomes.

Key words: albumin–hemoglobin–well-differentiated neuroendocrine tumour

1 INTRODUCTION:

Neuroendocrine tumours (NETs) are composed of by a wide range of neoplasm which mostly originate from neuroendocrine cells of gastrointestinal tract, pancreas or lungs. The incidence of NETs in United State was 6.98 cases per 100.000 people in 2012 according to SEER database. Despite its lower prevalence, the incidence rate showed a remarkable increase from 1973 to 2012[[1]. There are various factors that predict the outcome of disease; including primary tumour site, stage, grade, age, primary tumour size and lymph node involvement [2, 3]. Of those, stage and grade are well established prognostic factors directly correlating with survival [4, 5].

According to the latest classification of World Health Organization (WHO), NETs are graded as well-differentiated, low-grade (G1); well-differentiated, intermediate-grade (G2); poorly differentiated, high-grade (G3); and a fourth category for pancreatic neuroendocrine tumours: well-differentiated, high grade (G3) on the basis of Ki-67 proliferation index and mitotic count on high-power field (HPF). In 2017, WHO has further divided pancreatic grade 3 neuroendocrine tumours into well-differentiated and poorly-differentiated subgroups [6].

Different response rates and survival outcomes of NETs, even within the same group, might be attributed to its heterogeneous nature. There are number of studies in the literature to identify prognostic or predictive markers in NETs [7–10]. However, there are still no well-established

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prognostic factors except for Ki-67 proliferation index and mitotic count which are essential for grading. In the literature, numerous easy-accessible and simple markers, including inflammatory markers such as C-reactive protein, albumin, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume, gamma-glutamyltransferase (GGT) were reported to predict outcomes of the patients with NETs. The emerging data suggest that inflammatory response in tumour microenvironment has a role in determining the outcomes of the cancers [11]. Thereby, recent studies have been focused on the markers that might reflect the inflammatory response in tumour microenvironment [8–10].

In this study, we aimed to evaluate the prognostic value of inflammation markers specifically for the patients with well differentiated NETs involving only G1 and G2 NETs. We evaluated the inflammatory ratios (i.e neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, monocyte/lymphocyte ratio, GGT/lymphocyte ratio). Besides, we considered to evaluate all of the patients for albumin and hemoglobin concetrations together, since hypoalbuminemia and anemia have been reported to have poor prognostic effect on survival of different cancer types [12–16]. Therefore, we decided to use a novel parameter including both albumin and hemoglobin.

2 PATIENTS AND METHODS:

Patients and data:

We retrospectively reviewed the clinical records of the patients with well differentiated G1 and G2 NETs followed-up in our centre between June 2002 and November 2018. A total of 132 patients' data were reached and pooled from oncologic follow-up files in our centre. All patients were aged over 18 and had histologically confirmed well differentiated G1 and G2 NETs. Patients who had G3 tumours and second primary cancer were excluded from the study.

Various factors were gathered from the follow-up files including age at diagnosis, the Eastern Cooperative Oncology Group (ECOG) performance-status score, primary site of tumour, primary tumour size, presence of metastasis, progression-free survival (PFS), overall survival (OS), treatment modalities, and various parameters from laboratory test results which may have prognostic and/or predictive role (white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, haemoglobin concentration, albumin concentration, GGT concentration and alkaline phosphatase (ALP) at the time of diagnosis. Progression-free survival (PFS) was determined as the time between the beginning of treatment and first progression or death from any cause, whichever occurred first. Complete blood count analyses were performed from collected blood sample in ethylenediaminetetraacetic acid (EDTA) anticoagulated tubes. White blood cell count, lymphocyte and platelet count was recorded as number in per microliter, albumin and haemoglobin concentration was recorded as gr/dl. Multiplication of hemoglobin and albumin was recorded as a novel parameter and used in survival analyses.

Staging and grading:

Ki-67 proliferation index, mitotic count on high-power fields (HPF) and grade were recorded directly from pathology reports. The staging and grading of the disease were re-performed according to 8th edition of the AJCC Cancer Staging Manual and the latest update of WHO in 2017 [6] [17].

Statistical Analyses:

Statistical analysis was performed by using Statistical Package for the Social Sciences Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). We used Kaplan-Meier test for survival, and outcomes were analysed by Log-rank test. Overall survival was calculated from the date of diagnosis to date of last control for alive patients or death from any cause. Univariate and multivariate Cox proportional hazards regression analysis was used to assess the prognostic significance of the various parameters on OS. Cut-off values are extracted from receiver operating characteristic (ROC) analysis. A p-value <0.05 was considered as statistically significant.

3 RESULTS:

A total of 132 patients with well-differentiated G1 and G2 NETs were included in this study. The number of female patients was 81 (61.4%) and male patients was 51 (38.6%). Median age at the time of diagnosis was 53.0 years (22-80) for all cohort. In the whole group, 68 (51.5%) patients had G1 tumour and 64 (48.5%) patients had G2 tumours. The most common primary site was pancreas with a number of 44 (33.3%); the other locations were gastric, intestinal, appendix, rectum and others with a number of 30 (22.7%), 18 (13.6%), 10 (7.6%), 8 (6.1%) and 22 (16.7%), respectively. At the time of diagnosis, 105 (79.5%) patients had local disease and 23 (17.4%) patients had metastatic disease. Ninety-eight (74.2%) patients had surgery for primary tumour either with or without metastasectomy. Median follow-up period was 49.28 (1.7-186.2) months for all group. Median OS for whole group has not been reached yet. At the time of final analyses, the survival data of 7 patients could not have been reached, and the number of alive patients was 105 (79.5%) within the whole group. Patients characteristics are summarized in Table 1.

Multivariate analyses for OS showed that neutrophil/lymphocyte ratio (p=0.814), platelet/lymphocyte ratio (p=0.090), monocyte/lymphocyte ratio (p=0.115) and GGT/lymphocyte ratio (p=0.131) had no statistically significant effect on OS except for albuminXhemoglobin (AlbXHb) (HR=0.871, 95% CI 0.800-0.947, p=0.001). Additionally, the result of univariate analyses defined AlbXHb as a statistically significant prognostic factor for OS (HR=0.925 95% CI 0.878-0.974, p=0.003).

Median albumin and hemoglobin concentrations were 4.3 gr/dl (2.5-5.2) and 12.4 gr/dl (6.4-17.5) at diagnosis for whole group, respectively. The ROC analysis was performed to set a cut-off value for multiplication of albumin with hemoglobin. The ROC analysis was performed by using survival status as an endpoint and areas under curve (AUC)

Table 1. Chlinicopathologic features of all patients

Patients characteristics	No (%)
Age (years), median (range)	53 (22-80)
Gender	
Female	81 (61.4%)
Male	51 (38.6%)
ECOG score	
0-1	122 (92.4%)
≥2	10 (7.6%)
Tumour location	
Pancreas	44 (33.3%)
Gastric	30 (22.7%)
Intestinal	18 (13.6%)
Appendix	10 (7.6%)
Rectum	8 (6.1%)
Other	22 (16.7%)
Histological grade	
Grade 1	68 (51.5%)
Grade 2	64 (48.5%)
Stage	
Metastatic	23 (17.4%)
Local or locally advanced	109 (82.6%)
Surgery	
Yes	98 (74.2%)
No	34 (25.8%)
Treatments*	
Yes	22 (16.7%)
No	110 (83.3%)
Risk group	
High-risk	47 (35.6%)
Low-risk	70 (53.0%)
Missing	15 (11.4%)

Patients who receivedeither chemotherapy or somatostatin analogues

was 0.771 (95% CI 0.662-0.879) with statistical significance (p=0.001) Figure 1.

The maximal joint point of sensitivity and specificity was 47.94 which had sensitivity and specificity 80% and 66.3%, respectively. All patients with well-differentiated NETs (G1 and G2) were sub-grouped with respect to determined cut-off value. A total of 117 patients could have been categorized according to this scoring system: low risk group (AlbXHb ≥47.94, n:70, 53%) and high risk group (AlbXHb ≤47.94 n:47, 35.6%). Fifteen patients (11.4%) could not have been evaluated for AlbXHb due to absence of data either in albumin or hemoglobin concentration. There was no statistically difference for baseline clinicopathological features between high-risk and low-risk groups Table 2.

Overall survival of these two sub-groups was statistically different, demonstrated by using Kaplan-Meier method with log-rank test. Median OS was 135.5 months (95% CI 83.0-188.0) for high-risk group, while it has not been reached in low risk group (p=0.005)Figure 2.

The COX regression analysis showed that the patients in high risk group has increased risk of death compared to low risk patients (HR:5.16, 95%CI 1.45-18.38 p=0.011).

4 DISCUSSION:

Well-differentiated NETs are substantially heterogeneous tumours. Furthermore, disease course might differ even within the same grade tumours. The heterogeneity of NETs has not been well-understood until now. Therefore, novel prognostic and predictive factors are needed to explain its heterogeneity. However, recent studies are focused on simple and easy-accessible parameters to make an estimation about treatment response and disease course. Majority of these studies are based on the hypothesis that some plasma proteins and complete blood count parameters might reflect the tumour microenvironment. Various parameters, including inflammatory markers such as C-reactive protein, albumin, neutrophil, lymphocyte, platelet, hemoglobin, mean platelet volume, plasma levels of GGT and AST have been evaluated in those studies. In addition, these parameters have been studied not only in NETs but also in a wide range of tumours. Result of these studies demonstrated a correlation of those parameters with survival (OS, PFS) in spite of some inconsistencies.

In this study, we specifically focused on markers that might be used to figure out tumour microenvironment. Multivariate analyses showed a strong effect of albumin and hemoglobin concentrations on OS. Albumin and hemoglobin are definitely distinct parameters, however multiplication of them seems to correlate with survival. Furthermore, survival data of low-risk and high-risk patients according to AlbXHb confirmed the prognostic value of these novel parameter. Many studies have demonstrated a relation between oxidative stress and many diseases including cancer [18]. Reactive oxygen species (ROS) have ability to contribute carcinogenesis via induction of DNA damage, epigenetic changes, tumour heterogeneity and key activation factors, including NF-κB [18–20]. However, oxidative stress has dual effect on cancer progression with respect to its level. While lower levels of ROS promote carcinogenesis, proliferation and resistance to oxidative stress, higher levels of ROS can limit the proliferation capacity of cancer cells due to the lack of antioxidant metabolic products during metastasis [19]. There is a substantial association among oxidative stress, inflammation and carcinogenesis. They all promote each other by complex intracellular pathways which in turn cause an inflammatory state both in the tumour microenvironment and in the whole body [20]. Systemic inflammation results with reduced concentrations of albumin and hemoglobin through secretion of various inflammatory mediators. Additionally, hypoxia is an another state that promote angiogenesis and cell proliferation by hypoxia inducible factor-1 (HIF1), an oxygen-dependant transcription factor. Hypoxia inducible factor-1 (HIF1) is continuously produced and rapidly degraded in normoxic cells; on the contrary, degradation of HIF1 is decreased in hypoxic cells [20, 21]. The relation of plasma hemoglobin concentration with tumour oxygen status was demonstrated in several preclinical animal studies in which evaluation was performed on experimental tumours. These studies showed that tumour hypoxia was more prominent in anemic animals than in non-anemic ones [22].

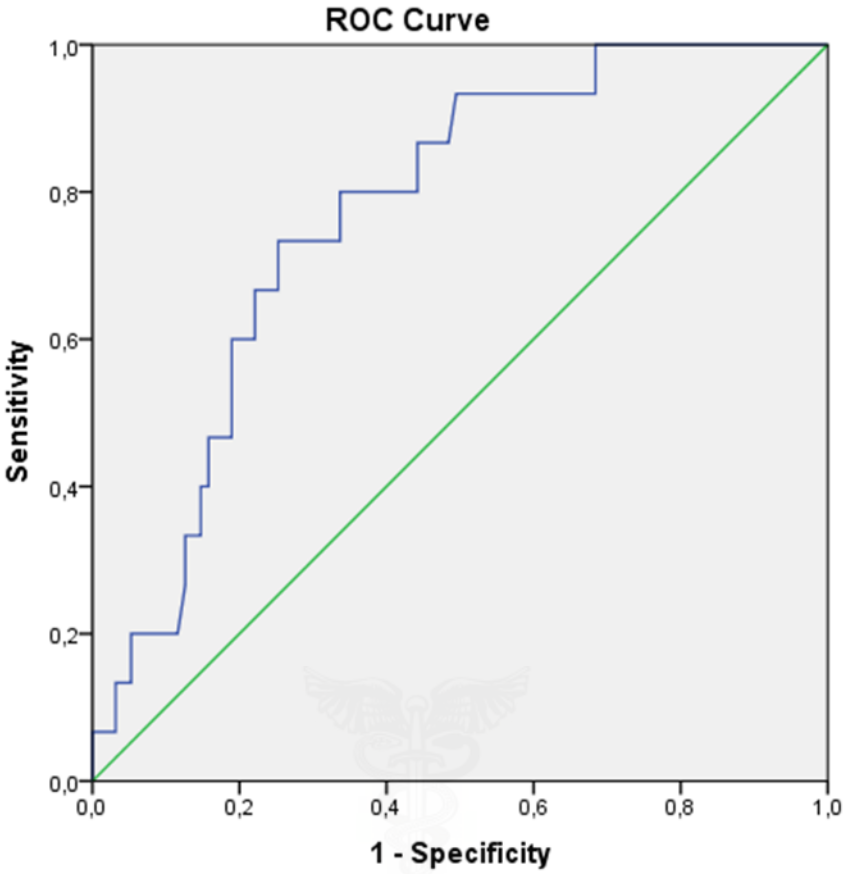

Figure 1. The area under curve (AUC) for AlbXHb in ROC analysis.

Table 2. Chlinicopathologic characteristics of the patients in high-risk* and low-risk subgroups**

Patients characteristics	High-risk group	Low-risk group	P-value
Age (years), median (range)	53 (22-78)	55 (24-80)	0.464
Gender			
Female	33 (70.2%)	40 (57.1%)	0.152
Male	14 (29.8%)	30 (42.9%)	
ECOG score			
0-1	42 (89.4%)	66 (94.3%)	0.481
≥2	5 (10.6%)	4 (5.7%)	
Tumour location			
Pancreas	12 (25.5%)	26 (37.1%)	0.442
Gastric	10 (21.3%)	18 (25.7%)	
Intestinal	6 (12.8%)	9 (12.9%)	
Appendix	5 (10.6%)	4 (5.7%)	
Rectum	3 (6.4%)	5 (7.1%)	
Other	11 (23.4%)	8 (11.4%)	
Histological grade			
Grade 1	20 (42.6%)	40 (57.1%)	0.122
Grade 2	27 (57.4%)	30 (42.9%)	
Treatments			
Yes	7 (14.9%)	10 (14.3%)	0.927
No	40 (85.1%)	60 (85.7%)	

* Patients with AlbXHb<47.94

**Patients withAlbXHb>47.94

Patients who received either chemotherapy orsomatostatin analogues

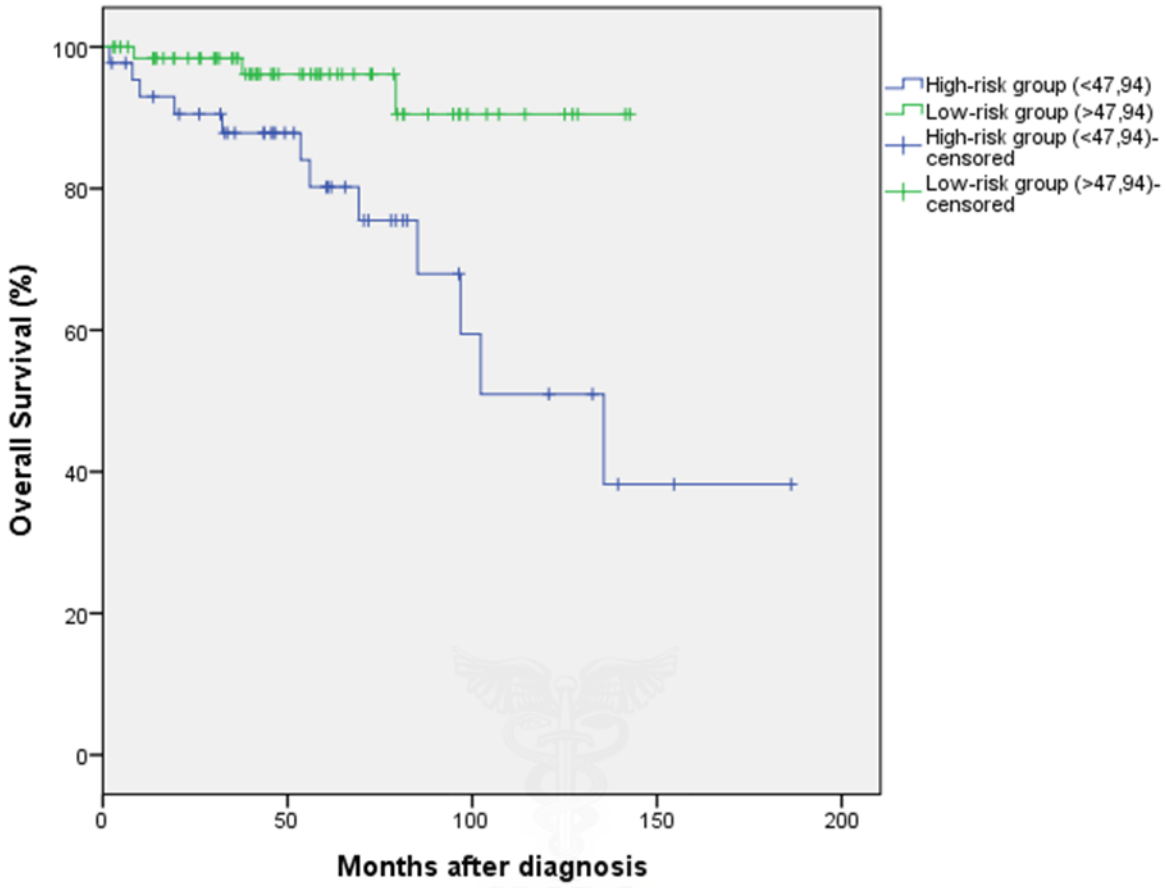

Figure 2. Kaplan-Meier survival curves for the low-risk and high-risk group.

The rationale for using both albumin and hemoglobin concentrations was based on hypothesis that these markers can reflect the tumour microenvironment and aggressiveness indirectly. Since albumin and hemoglobin concentrations are definitely distinct entities, we considered to multiply them and find out a cut-off value for multiplication to increase the statistical meaning. We determined that this novel parameter, AlbXHb, could predict the survival of patients with high sensitivity and specifity. The prognostic value of albumin and hemoglobin was demonstrated separately for various cancer types, despite the fact that they were not evaluated together. In these studies, lower albumin and hemoglobin concentrations were associated with poor prognosis [14, 16].

However, to best of our knowledge, there are no trials searching the accuracy of prognostic factors specifically for the patients with well-differentiated NETs. *Zhou et al* showed the prognostic significance of GGT/lymphocyte ratio in a study which included 125 patients with only non-functional pancreatic NETs [9]. In our study, GGT/lymphocyte ratio was not statistically significant parameter either in univariate analyses or multivariate analyses. This difference might be related to heterogeneity of the study population. *Zou J et al* aimed to find out inflammation based prognostic factors and revealed a new scoring system in a study which included patients with advanced and metastatic NETs. This scoring system was a combination of Glasgow Prognostic Score, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, high-sensitivity inflammation-based prognostic index and prognostic nutritional index [8]. On the contrary of that study, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio failed to predict disease outcome or survival. However, majority (70.3%) of patients had G3 NETs and it might have contributed to this difference.

In conclusion; well-differentiated NETs is an area of deserving more further studies, although they are 'orphan' tumours. Due to its heterogeneity, there are many uncertainty about prognosis, management and classification. There is little data exist about well-differentiated NETs in the literature. Thereby, in this study, we aimed to develop a novel and simple parameter, AlbXHb, which can be used to predict OS of the patients with well-differentiated NETs. This novel parameter, AlbXHb, has statistically significant accuracy for prediction of outcome in this specific patient population. On the other side, major limitation of our study is its retrospective nature. Finally, we considered our results

need to be confirmed by further prospective clinical trials with larger number of patients.

Disclosure Statement: The authors have no conflicts of interest to declare.

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