Original Article

Nutritional index for immune-checkpoint inhibitor in patients with metastatic gastro-esophageal junction/gastric cancer

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Background: Nutritional status is strongly associated to prognosis in metastatic gastrooesophageal junction (mGOJ)/gastric cancer (GC) patients. The aim of the present study was to develop an immune-checkpoint inhibitor (ICI)-specific nutritional index (NI).

Methods: Ten serum and anthropometric nutritional markers derived from blood tests or CT scans were analyzed at baseline in patients treated with second-line ICI and correlated with overall survival (OS). An ICI-specific NI (the NUTRIICI) was developed with its specificity assessed in an independent group of patients treated with standard second-line chemotherapy.

Results: From June 2014 to December 2018, 57 mGOJ/GC patients (14 females, 43 males) with a median(m) age of 61 years (range 29–85) received ICI as second-line therapy (Pembrolizumab n=26, Nivolumab n=16, Avelumab n=15). Among the 10 analyzed variables, Onodera's prognostic NI (PNI) ≤33 and waist-to-hip (WHR) <1 were independent predictors of OS and used to build the NUTRIICI. Patients with both favorable factors (i.e., PNI >33 and WHR ≥1, comparator group) had a mOS of 18.0 *vs.* 6.7 months of patients with one unfavorable factor (either PNI ≤33 or WHR <1, Hazard Ratio, HR 3.06), *vs.* 1.3 months of patients with both unfavorable factors (HR 17.56), overall P<0.0001. In the independent group of patients treated with standard chemotherapy NUTRIICI was not associated with prognosis (P=0.57).

Conclusions: NUTRIICI is the first ICI-specific NI for mOGJ/GC patients receiving second-line ICI. A validation in larger cohorts is strongly encouraged.

Keywords: Gastric cancer; immunotherapy; nutrition

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Introduction

Malnutrition occurs in up to 80% of metastatic gastro-oesophageal junction (mGOJ)/gastric cancer (GC) patients (1,2). It is usually caused by the mechanical effect of the primary tumor that gives onset to symptoms such as dysphagia and early satiety, or by the reduction of food intake as part of the systemic cachexia (3-6). Nutritional support (oral, enteral or parenteral) is recommended in both the postoperative and advanced disease settings, given its favorable impact on prognosis, anticancer therapy compliance and quality of life (7).

The well-known Onodera's Prognostic Nutritional Index (PNI), which takes into account serum albumin and total lymphocyte count, was previously studied to evaluate the nutritional status of GOJ/GC patients in both the post-operative and the metastatic settings and proved to be an independent prognostic factor (8-11).

Nivolumab and Pembrolizumab have recently been approved for the treatment of mGOJ/GC patients in several regions including Asia, Europe and Unites States, and approval has also been obtained for nivolumab as adjuvant treatment in resected oesophageal cancer patients (12-15). Nevertheless, analyses would be desirable to identify specific predictors of immune-checkpoint inhibitor (ICI) efficacy.

Tissue PD-1 combined positive score (CPS) is the most widely investigated marker for response and survival. However, there are challenges in terms of the ideal CPS cut off (i.e., >1%, >5% and >10%) to be adopted. In addition, different bioassays and different scoring systems [such as tumor positive score (TPS) *vs.* CPS] have been used which make it challenging to carry out cross-trial comparison.

The nutritional status and adipose tissue volume have both been reported to impact on immune response. Wang *et al.* have recently demonstrated, in a variety of tumors, that enlarged visceral adipose tissue might induce an immunosuppressive status in T lymphocytes via the over-expression of PD-1 on their surface. This could potentially predict increased efficacy of anti PD-1 agents (16-18).

The aim of the present study was to assess whether an ICI-specific nutritional index, inclusive also of a visceral adipose tissue marker such as waist-to-hip ratio (WHR), would be superior to classic nutritional indexes (such as Onodera's PNI) in predicting survival in mGOJ/GC patients treated with second-line ICI.

We analyzed easily obtainable nutritional/inflammatory factors to render the index readily available. An ICI-specific NI would both help selecting patients more likely to benefit from immunotherapy and guide targeted nutritional interventions for patients with worse prognosis. We present the following article in accordance with the REMARK reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-217/rc).

Methods

Study design

Our study is a retrospective case-control study with an age- and gender-matched control cohort. The number of cases meeting the inclusion criteria during the study period determined the sample size. The primary objective was to correlate nutritional markers with overall survival (OS), defined as the time from the ICI start (or the second line chemotherapy start in the control group) to death from any cause. Patients who did not reach the death endpoint were censored at the last known follow-up date. Tissue PD-L1 expression status was not available for the majority of the patients and therefore not included in the analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Sarah Cannon Research Hospital and "Tor Vergata" University Hospital as part of protocol investigating the role of BMI in solid tumors (No. NCT03873064) and individual consent for this retrospective analysis was waived.

Patients

Eighty-nine patients with histologically confirmed GOJ/GC and measurable metastatic disease resistant to standard first-line fluoropyrimidine/platinum-based chemotherapy treated at the Sarah Cannon Research Institute (UK) or University College London Hospital between June 2014 and December 2018 were retrospectively reviewed. Only patients that were treated with second line ICI were included in the final analysis. Patients could receive either pembrolizumab, nivolumab or avelumab).

A same size gender- and age-matched control cohort of mGOJ/GC patients treated with standard paclitaxel- or fluoropyrimidine-based second-line chemotherapy was also analyzed by screening 109 patients treated between November 2014 and June 2019 at the "Tor Vergata" University Hospital of Rome, to confirm the ICI-specificity of the nutritional markers found significant in the ICI-treated cohort.

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Specimen characteristics

Baseline blood samples were obtained from all patients prior to treatment start. Routine chemistry studies, including lymphocyte count (10^9/L), serum albumin (g/dL), serum proteins (PRO, g/dL), blood glucose (mmol/L), albumin/globulin ratio (AGR) were performed on fresh samples within one hour from blood withdrawal. Processed blood sample were aliquoted and stored at –80 ℃ for any eventual further re-evaluation. Storage conditions were carefully maintained and all aliquots were limited to one freeze-thaw cycle.

Assessment of anthropometric nutritional indexes

Data on anthropometric nutritional markers at baseline (within one week before ICI start) were collected: height (in meters), body mass Index (BMI) [weight in kilograms divided by the square of height in meters (kg/m^2)], Onodera's PNI (i.e., serum albumin (g/dL) + 5 × total lymphocytes count (10^9/L) (19), sagittal diameter (using the L4-L5 baseline computed tomography (CT) cross-sectional image, distance from skin to skin through the center of the abdomen) and WHR (waist circumference using the L3 baseline CT cross-sectional image, perimeter at the L3 region divided by hip circumference).

All measurements were ascertained while blinded to the sample origin and to study endpoint.

Statistical analysis

All continuous variables were dichotomized by using the maximally selected rank statistics for overall survival (20) and differences in frequency of variable categories between the ICI and the control cohort were assessed by means of the chi-square test.

Univariate association of categorized variables and OS was examined using the Kaplan-Meier method with long rank test to assess for difference between subgroups, while univariate hazard ratios (HRs) with relevant 95% confidence interval (95% CI) were estimated by using the Cox proportional hazards regression.

Only variables found significant at the univariate analysis were included in a multivariable Cox-regression model to identify independent nutritional predictors of OS.

Significant variables were combined to create a NUTRItional Index for ICI (NUTRIICI) whose ICI-specificity was subsequently tested in the chemotherapy-treated control cohort.

All analyses were performed with the R software v. 4.0.2 and MedCalc software version 19.1.17. All tests were considered statistically significant for two tail P values <0.05.

Results

Baseline characteristics

A total 114 patients entered the study. Fifty-seven (14 females, 43 males) out of 89 screened patients were included in the ICI cohort. Median age 61 years (range, 29–85). Patients had lymph node metastasis (with or without other sites of metastasis) in 77% of cases, 23% of patients had non-lymph node metastasis, mainly in the liver and peritoneum. All the patients received previous treatment with platinum-based and fluoropyrimidine-based chemotherapy regimens, including regimens with anthracycline [32 (56.1%)]. Doublet or triplet first-line regimen had no impact on OS (P=0.38). All HER2 overexpressing patients [11 (19.3%)] received trastuzumab combined with platinum and fluoropyrimidine. Pembrolizumab, nivolumab and avelumab were the administered ICI for 26, 16 and 15 patients, respectively. OS endpoint was reached for 48 out of 57 patients. Median follow-up of the 9 patients censored at the end of the follow-up was 27 months (4 to 53 months). Median OS (mOS) of the entire cohort was 6.2 months (95% CI: 4.4–10.9 months), radiological response rate was 16%.

Variables were categorized according to the maximally selected rank statistics for overall survival as follow: height (<1.75 or ≥1.75 m), BMI (≥30 or <30), WHR (<1 or ≥1), sagittal diameter (<25 or ≥25 cm), lymphocytes (<1×10^9 or ≥1×10^9/L), blood sugar (<5 or ≥5 mmol/L), albumin (<30 or ≥30 g/dL), PRO (<60 or ≥60 g/dL), AGR (<1.5 or ≥1.5), Onodera's PNI (≤33 or >33). *Table 1* reports the frequency of the variable categories within the group.

Selected nutritional markers

All candidate nutritional markers were first evaluated in a univariate Cox regression analysis for overall survival (*Table 2*).

Among all variables, WHR, albumin, PRO and PNI were found to be significantly associated with survival, with the following HR and P value, respectively: 3.54 (95% CI: 1.38 to 9.10), P=0.009; 2.08 (95% CI: 1.07 to 4.05), P=0.03; 2.96 (95% CI: 1.43 to 6.12), P=0.003; 5.28 (95% CI: 2.34 to 11.92), P=0.0001.

The four markers found to be significant at the univariate analysis were assessed in a multivariate Cox regression model. In the multivariate analysis only WHR and PNI retained the statistical significance as independent

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Table 1 Characteristics of patients with GOJ/GC treated with ICIs

Characteristic	Range or n (%)
Height (m)	
Range	1.55–1.93
<1.75	22 (39%)
≥1.75	35 (61%)
BMI (kg/m^2)	
Range	15.8–36.4
<30	50 (88%)
≥30	7 (12%)
WHR	
Range	0.74–1.15
<1	51 (89%)
≥1	6 (11%)
Sagittal diameter (cm)	
Range	13.0–31.6
<25	44 (77%)
≥25	13 (23%)
Lymphocytes (×10^9/L)	
Range	0.2–2.8
<1	18 (32%)
≥1	39 (68%)
Glucose (mmol/L)	
Range	3.9–12.6
<5	11 (19%)
≥5	46 (81%)
Albumin (g/dL)	
Range	23–48
<35	12 (21%)
≥35	45 (79%)
PRO (g/dL)	
Range	47–82
<60	12 (21%)
≥60	45 (79%)
AGR	
Range	0.8–3.6
<1.5	23 (40%)
≥1.5	34 (60%)
Onodera's PNI	
Range	29.5–57.1
≤33	10 (18%)
>33	47 (82%)

GOJ/GC, gastro-oesophageal junction/gastric cancer; BMI, body mass index; WHR, waist-to-hip ratio; PRO, total serum proteins; AGR, albumin to globulin ratio; PNI, prognostic nutritional index.

predictors for OS (HR 3.75, 95% CI: 1.44–9.72, P=0.007 and HR 8.13, 95% CI: 1.39–47.48, P=0.02, respectively) and were used to build the NUTRIICI (*Table 2*).

NUTRIICI and survival analysis

By combining WHR and PNI, we assessed a potential nutritional prognostic index predictive of survival for mGOJ/GC patients treated with second-line ICI (NUTRIICI).

Patients were divided into three groups: patients with both favorable factors, i.e., WHR ≥1 and PNI >33 (8 patients); patients with one unfavorable factor, either WHR <1 or PNI ≤33 (40 patients); patients with both unfavorable factors, i.e., PNI ≤33 and WHR <1 (9 patients). Distinct survival probabilities were obtained for these three patient subgroups with median OS of 18.0, 6.7 and 1.3 months, respectively, overall P value <0.0001 (*Figure 1*).

Taking as reference patients with both favorable factors, HR was 3.06 (95% CI: 1.17 to 7.98), P=0.02 and 17.56 (95% CI: 5.25 to 58.69), P<0.0001, for patients with one and two unfavorable factors, respectively.

Assessment of nutritional markers and NUTRIICI in the chemotherapy-treated control cohort

In the chemotherapy control cohort, 57 patients (14 females, 43 males) with mGOJ/GC were included. Median age was 61 years (range, 33–87) and 51 patients reached the OS endpoint. Median follow-up of censored patients was 12.3 months (4 to 18.2 months). Patients had lymph node metastasis (with or without other sites of metastasis) in 70% of cases, 30% of patients had non-lymph node metastasis, mainly in the liver and peritoneum. All the patients received previous treatment with platinum-based and

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Table 2 Univariate and multivariate analyses of variables assessing for impact on OS in ICI-treated cohort

Characteristic	Univariate Cox regression analysis, HR (95% CI), P value	Multivariate Cox regression analysis, HR (95% CI), P value
Height (m) (<1.75/≥1.75)	1.37 (0.76 to 2.47), 0.28	
BMI (kg/m^2) (<30/≥30)	1.90 (0.91 to 3.98), 0.09	
WHR (<1/≥1)	3.54 (1.38 to 9.10), 0.009	3.75 (1.44 to 9.72), 0.007
Sagittal diameter (cm) (<25/≥25)	0.66 (0.34 to 1.26), 0.21	
Lymphocytes (×10^9/L) (<1/≥1)	0.70 (0.35 to 1.39), 0.31	
Glucose (mmol/L) (<5/≥5)	1.36 (0.68 to 2.72), 0.38	
Albumin (g/dL) (<35/≥35)	2.08 (1.07 to 4.05), 0.03	1.77 (0.53 to 5.89), 0.35
PRO (g/dL) (<60/≥60)	2.96 (1.43 to 6.12), 0.003	1.10 (0.34 to 3.61), 0.87
AGR (<1.5/≥1.5)	0.56 (0.30 to 1.04), 0.07	
Onodera's PNI (≤33/>33)	5.28 (2.34 to 11.92), 0.0001	8.13 (1.39 to 47.48), 0.02

OS, overall survival; ICI, immune-checkpoint inhibitor; BMI, body mass index; WHR, waist-to-hip ratio; PRO, total serum proteins; AGR, albumin to globulin ratio; PNI, prognostic nutritional index; HR, hazard ratio.

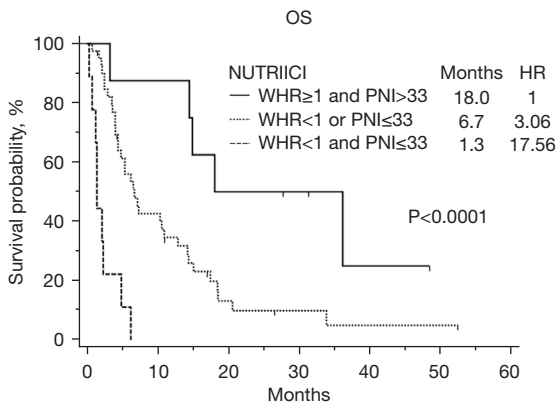

Figure 1 Three classes risk—NUTRIICI index and OS in ICI treated cohort. Both unfavorable factors: WHR <1 and PNI ≤33; one favorable factor: WHR <1 or PNI ≤33; both favorable factors: WHR ≥1 and PNI >33. PNI, prognostic nutritional index; WHR, waist-to-hip ratio; OS, overall survival; ICI, immune-checkpoint inhibitor.

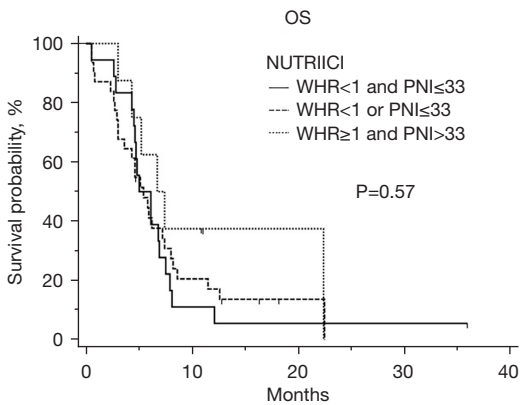

Figure 2 Three classes risk—NUTRIICI index and OS control cohort. Both unfavorable factors: WHR <1 and PNI ≤33; one favorable factor: WHR <1 or PNI ≤33; both favorable factors: WHR ≥1 and PNI >33. PNI, prognostic nutritional index; WHR, waist-to-hip ratio; OS, overall survival.

fluoropyrimidine-based chemotherapy regimens, including regimens with anthracycline [7 (12%)]. No statistically significant difference was observed in OS between patients treated with doublet *vs.* triplet first-line regimens (P=0.06). Trastuzumab was administered in HER2 positive cases [11 (19,1%)]. The second-line regimen was paclitaxel-ramucirumab for 19 patients and fluoropirimidine-based doublet for 23 patients. Fifteen patients received other chemotherapy regimens. mOS in this cohort was 6.4 months (95% CI: 0.1 to 22.4 months), radiological response rate with second-line chemotherapy was 12%.

By applying the NUTRIICI in the control cohort, 8 patients had both favorable factors, 31 one unfavorable factor, and 18 both unfavorable factors. No differences were observed in terms of survival according to the three NUTRIICI subgroups in the chemotherapy cohort (P=0.57), thus suggesting that NUTRIICI was specific for patients treated with ICI (*Figure 2*).

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Table 3 Distribution of 10 nutritional variables in patients with mGOJ/GC treated with standard chemotherapy and test for difference with the ICI cohort

Characteristic	Range or n (%)	Difference with the ICI cohort (chi-square test), P value
Height (m)		0.45
Range	1.55–1.80	
<1.75	26 (46%)	
≥1.75	31 (54%)	
BMI (kg/m^2)		0.08
Range	12.6–34.6	
<30	55 (96%)	
≥30	2 (4%)	
WHR		0.41
Range	0.70–1.60	
<1	48 (84%)	
≥1	9 (16%)	
Sagittal diameter (cm)		0.23
Range	14.5–28.7	
<25	49 (86%)	
≥25	8 (14%)	
Lymphocytes (×10^9/L)		0.43
Range	0.2–3.7	
<1	22 (39%)	
≥1	35 (61%)	
Glucose (mmol/L)		0.09
Range	3.5–10.6	
<5	19 (33%)	
≥5	38 (67%)	
Albumin (g/dL)		0.20
Range	20–44	
<35	18 (32%)	
≥35	39 (68%)	
PRO (g/dL)		0.06
Range	33–74	
<60	21 (37%)	
≥60	36 (63%)	
AGR		0.57
Range	0.4–3.6	
<1.5	26 (46%)	
≥1.5	31 (54%)	
Onodera's PNI		0.06
Range	20.0–44.1	
≤33	19 (33%)	
>33	38 (67%)	

mGOJ/GC, metastatic gastro-oesophageal junction/gastric cancer; ICI, immune-checkpoint inhibitor; BMI, body mass index; WHR, waist-to-hip ratio; PRO, total serum proteins; AGR, albumin to globulin ratio; PNI, prognostic nutritional index.

Looking at the variable category frequencies within the chemotherapy cohort, we did not find any significant difference as compared to the ICI cohort, chi-square P values ranging from 0.06 to 0.57 (*Table 3*).

At the univariate Cox regression analysis for OS in the chemotherapy cohort, only the total serum protein level was found to be significantly associated with survival: HR 2.23 (95% CI: 1.24 to 4.00), P=0.007, taking PRO >60 gr/dL as reference.

Discussion

Immune-checkpoint inhibitors have changed the prognosis and the treatment strategy for many cancer patients. However, there are still great challenges for clinicians to identify predictors of ICI efficacy, in particular as clinical or laboratory biomarkers.

Several real-world data of the prognostic factors in mGOJ/GC patients treated with ICI have been published in the last years. Sato *et al.* recently analyzed a large cohort of more than 200 Japanese heavily pretreated GC patients receiving Nivolumab (21). They found that C-reactive protein (CRP) <0.5 mf/dL, immune-related adverse events, albumin >3.5 g/dL, performance status 0, lymphocyte count >1,000/μL, and differentiated pathological type were independently associated with improved survival in multivariate analysis. Moreover, by dividing patients in 3

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groups, according to the presence of 0 to 6 risk factors at baseline, different OS were obtained (P<0.001).

The nutritional status is one of the most important clinical aspects for GOJ/GC patients. It is regularly assessed during the treatment of these patients; nevertheless, little is known about the impact of the nutritional status on the efficacy of immunotherapy. Moreover, only a few small studies have evaluated nutritional indexes in standard chemotherapy-treated mGOJ/GC patients, with these indexes being mostly based on inflammation parameters (i.e., CRP), all of them in pan-Asian cohorts (21-24).

We analyzed 10 nutritional measures in a well selected set of mGOJ/GC patients treated with second-line ICI monotherapy and found that high Onodera's PNI (>33) and WHR (>1) were the most significant nutritional predictors of better survival. These two variables were used to build the NUTRIICI.

Onodera's PNI is a traditional 'immune-nutritional' parameter, initially used to predict prognosis in patients undergoing surgery for gastrointestinal cancer (19). It combines the serum albumin, a proxy of nutritional status and a marker of stem-cell differentiation and apoptosis (25-28), and the total lymphocyte count, that is known to be positively associated with response to chemotherapy and survival in mGOJ/GC (29,30). Hypoalbuminemia especially is commonly studied alone (21) or in combination with other lab values as neutrophil-to-lymphocyte ratio, CRP (31), serum lactate dehydrogenase (32) or total cholesterol level (33) as a negative predictor of treatment outcome in mGOJ/GC patients treated with anti-PD-1 agents. In our work, albumin level confirmed its prognostic value in univariate but not in multivariate analysis, while PNI retained significance value at P<0.05.

Namikawa *et al.*, have previously analyzed the role of PNI in a small retrospective cohort of 27 Asian mGC patients treated with the anti-PD-1 agent nivolumab (34). They conducted a simple univariate analysis and found that higher PNI, together with lower neutrophil-lymphocyte ratio (NLR), higher Glasgow Prognostic Score (GPS) and occurrence of Immune-related adverse events (irAEs), were predictive of increased radiological response rate and longer survival (34). Median baseline PNI reported in this series was comparable to the that found in our cohort (32.1 *vs.* 33). PNI of 33 can thus be considered an adequate cut-off value in this setting.

Our results, besides underlining the importance of nutritional status and systemic inflammation as measured by PNI, also highlight the relationship between visceral adiposity and ICI efficacy.

We assessed for the first time in ICI-treated mGOJ/GC patients the anthropometric parameter WHR, which is a measure of abdominal obesity originally tested as prognostic marker in patients with heart failure and other cardiovascular diseases (35).

In patients with cancer, WHR has been previously evaluated in relation to the risk of developing gastric, breast, colorectal and prostate cancer, but data on its role as prognostic and predictive marker in patients with advanced disease are limited (36-40). In our study we found no significant prognostic role of WHR in the cohort of patients treated with chemotherapy (P=0.81), while demonstrating a significant association with survival in both the univariate and multivariate analysis in the ICI-treated cohort. To the best of our knowledge, this is first time that a visceral adiposity marker is found to be predictive of survival in ICI-treated patients. Previous studies have focused on the role of classic BMI as a parameter of obesity. In ICI-treated melanoma and kidney cancer patients a correlation between BMI and progression free survival and overall survival has been found in retrospective series (40-49), however BMI is considered inadequate to capture the overall complexity of obesity (50).

BMI is suboptimal as a measure of visceral and subcutaneous adipose tissue, since it does not take into account the whole-body composition made by fluids, muscle and lean masses. Contrary to WHR, BMI was not found to correlate with survival in our analysis (P=0.09), thus suggesting that markers that more precisely recapitulate the abundance of visceral adipose tissue have a superior performance in terms of survival prediction in ICI-treated patients.

The combined analysis of Onodera's PNI and WHR was used to build a new prognostic nutritional tool (NUTRIICI), that was demonstrated to be ICI-specific in mGOJ/GC (P=0.57 in the chemotherapy cohort) and with very high statistical significance (P<0.0001) (23,51).

Nonetheless, we acknowledge a number of limitations in our study. Above all the limitations is the retrospective design of the study. Moreover, data on concomitant medications or other medical conditions, that are known to possibly influence both the inflammation and the nutritional status, were not part of the analysis. Furthermore, the analysis was conducted on a relatively small sample size with unknown PD-L1 status. PD-L1 is a widely recognized tissue marker in ICI-treated patients, its integration in the analysis would have clarified the role of NUTRIICI

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in relation to established tissue immune variables. Finally, WHR was manually derived from available CT scans by gating waist and hip circumferences. An automatic measurement of WHR would be desirable to minimize operator-dependent errors in the analytic process.

In conclusion, NUTRIICI is the first ICI-specific nutritional index for mGOJ/GC patients. NUTRIICI has confirmed the strength of Onodera's PNI as a prognostic marker but also underlined the importance of WHR as a measure of visceral adipose tissue volume. A prospective validation of NUTRIICI is strongly warranted.

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Footnote

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Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-217/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-217/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Sarah Cannon Research Hospital and "Tor Vergata" University Hospital as part of protocol investigating the role of BMI in solid tumors (No. NCT03873064) and individual consent for this retrospective analysis was waived.

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