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Original Article

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Risk Factors Predicting Outcomes in Advanced Upper Gastrointestinal Cancers Treated With Immune Checkpoint Inhibitors

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have moved to the frontline in recent years to manage upper gastrointestinal (UGI) tumors, such as esophageal and gastric cancers. This retrospective review sheds light on real-world data on ICI-treated UGI tumors to identify risk factors (clinical and pathological) impacting the outcome other than traditional biomarkers (programmed cell death ligand 1 (PD-L1) or microsatellite instability status).

Methods: Patients with UGI tumors who received at least one dose of ICI for stage IV or recurrent disease between January 1, 2015, and July 31, 2021, at The Ohio State University were included in the study. The patients' baseline characteristics, labs, and blood counts (even at disease progression) were extracted with survival outcomes (progression-free survival (PFS) and overall survival (OS)). Descriptive statistics, log-rank test and Cox proportional hazard model for survival outcomes, Fisher exact test for categorical variables, were conducted using JMP Pro 16 (SAS Institute Inc., Cary, NC).

Results: We had 64 patients (84% males) included in the study, with the racial distribution as follows: 88% Caucasian, 5% African American, 1% Asian, and 6% from other racial groups. Men and the use of ICI in third lines or more had a positive impact on PFS and OS. For OS, 1) history of surgery positively impacted the outcome, while bone metastases worsened it; 2) baseline red blood cell count (RBC), hemoglobin, and thyroid-stimulating hormone (TSH) negatively impacted the OS. For PFS, 1) PD-L1 positivity, baseline lymphocyte count, and aspartate transferase levels had a positive impact; 2) human epidermal growth factor receptor 2 (HER2) positivity, baseline RBC, TSH, alkaline phosphatase, and alanine transferase (AST) levels had a negative impact. A slight increase in white blood cell (WBC) count (by 1.54, P = 0.02) and a drop in lymphocyte count (by 0.1907, P = 0.003) was significantly associated with disease progression.

Conclusions: Baseline risk factors and monitoring blood counts can help predict outcomes in ICI-treated UGI tumors. We need larger studies to confirm this.

Keywords: Immune checkpoint inhibitors; Esophageal cancer; Gastric cancer; Immunotherapy; Biomarkers; Prognostic marker; Immunotherapy

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Introduction

Immune checkpoint inhibitors (ICIs) have become a key component of advanced upper gastrointestinal (UGI) tumors in recent years, with approvals following the success of clinical trials such as KEYNOTE 590, CheckMate 649 and KEYNOTE 811 [1, 2]. ICIs were reserved for microsatellite instability-high (MSI-H) patients in second- or third-line post-chemotherapy before moving to the first line [3-9].

Since 2021, the chemotherapy-ICI combination in the first line has been universally accepted as the standard of care (SOC) for eligible advanced microsatellite-stable (MSS) UGI adenocarcinoma patients. The UGI ICI management, especially adenocarcinomas, is dominated by programmed death-1 (PD-1) inhibitors such as nivolumab and pembrolizumab. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors such as ipilimumab are used in combination with PD-1 inhibitors (nivolumab) to treat squamous cell esophageal cancers [10]. Treatment selection is based on programmed cell death ligand 1 (PD-L1) and human epidermal growth factor receptor 2 (HER2) expression levels in

the tumor samples. In the recent update from Check-Mate 649 after 36.2 months follow-up, the addition of nivolumab to chemotherapy (combination of 5-flurouracil and oxaliplatin (FOLFOX) or combination of capecitabine and oxaliplatin (CAPOX)) in HER2-negative patients with PD-L1 combined positive score (CPS) ≥ 5 had a better 3-year survival rate (21% vs. 10%), overall survival (OS, 14.4 vs. 11.1 months, hazard ratio (HR) = 0.70), progression-free survival (PFS, 8.3 vs. 6.1 months, HR = 0.70), duration of response (9.6 vs. 7 months), and objective response rate (ORR, 60% vs. 45%) than chemotherapy alone [11]. This benefit was maintained in all the patients irrespective of PD-L1 level and followed the same trend reported in the previous publication in 2021. Similarly, adding pembrolizumab to chemotherapy improved OS in patients with CPS ≥ 10 in the KEYNOTE 859 trial for the same population. In HER2-positive tumors, combining pembrolizumab, chemotherapy, and trastuzumab was beneficial only to patients with CPS ≥ 1 (PFS: 11 vs. 7 months, HR = 0.71; OS: 20 vs. 16 months, HR = 0.81; ORR: 73% vs. 58%) [12]. ICI is not currently recommended for HER2-negative CPS < 5, and HER2-positive CPS < 1 patients.

In an era when advanced genomic testing tools such as comprehensive mutational profiling and RNA sequencing are available, relying on traditional immunohistochemistry (IHC)-based biomarkers is disheartening. We do not know the patient population that benefits from ICI beyond MSI-H status and PD-L1 expression level. Tumor heterogeneity and interpersonal bias in reading the PD-L1 level are concerning factors for treating physicians. Identifying reliable risk factors and biomarkers from the baseline patient (age, gender, and race) and tumor characteristics (PD-L1 level, MSI-H status, HER2 -status, stage of ICI use, number/location of the metastases, and prior therapy), and routine lab investigations could provide a simple model to the physician to assess the benefit of ICI in the clinic. Models that do not require complex tests accompanied by financial toll (RNA-sequencing, comprehensive genomic profiling, and cell-free DNA testing) could be easily adopted everywhere. This knowledge will help in adopting other forms of immunotherapy in the early stages for solid tumors, such as chimeric antigen receptor (CAR) T-cell therapy and tumor-infiltrating lymphocytes (TILs) quicker into clinical practice.

This study investigated UGI (esophageal and gastric) adenocarcinomas treated with ICI alone or combined with chemotherapy at various advanced-stage lines to identify the risk factors and biomarkers associated with outcomes. We also studied the difference in lab parameters that could predict disease progression.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of The Ohio State University (protocol number 2021C0133 and date of approval: September 3, 2021).

Patient selection and chart review

After receiving appropriate Institutional Review Board approvals, The Ohio State University's electronic health records (January 2015 through July 2021) were searched using the diagnosis code from the International Statistical Classification of Diseases (ICD) 10th version (i.e., the ICD-10 code) and the ICI drug names. All the present study procedures were conducted in compliance with the Helsinki Declaration for research on human beings. Patients included in this study had a diagnosis of UGI adenocarcinoma (esophageal, gastroesophageal junction, and gastric) and received at least one dose of ICI in the study period. We excluded the patients with squamous cell carcinoma. During the study, patient selection and management followed the standard-of-care protocols. Towards the end of the study period, ICIs were approved for use in combination with chemotherapy as a first-line treatment, while in the early part of the study, they were approved for use in subsequent lines of therapy.

Data extracted through chart review (retrospectively) included demographics (such as age, race, and sex), tumor-related clinicopathological data (such as type of the primary malignancy, stage of ICI use, number of metastatic sites, and prior therapy), and lab data (such as complete blood counts, including total white blood cells (WBC), red blood cells (RBC), absolute neutrophilic count (ANC), absolute lymphocyte count (ALC), platelet count, and hemoglobin and chemistries including total bilirubin (TBil), albumin, alkaline phosphatase (ALP), alanine transferase (ALP), aspartate transferase (AST)).

Statistical analysis

We conducted a comprehensive statistical analysis to identify any potential associations between patient characteristics and survival outcomes, including PFS, OS, and ICI-related overall survival (OS-ICI). PFS was defined as the time between the first dose of ICI and disease progression. OS was defined as the date of diagnosis to the date of death or the last follow-up date. OS-ICI was defined as the date of the first dose of ICI to the date of death or the last date of follow-up. This distinction (OS vs. IS-ICI) was made to understand better the benefit of ICI with subsequent therapy for survival. Descriptive statistics were employed to summarize the baseline characteristics of the study population. To analyze survival data, we used the Cox proportional hazard model, a semi-parametric method that estimates the risk of an event, such as disease progression or death, over time, given specific variables. This model is based on the proportional hazards assumption, which states that the HRs for the covariates remain constant over time. HRs with 95% confidence intervals (CIs) were calculated to assess the impact of each covariate on survival outcomes. To compare survival curves between different patient groups, we used the log-rank test, a non-parametric test that evaluates the statistical significance of differences in survival between groups. For categorical variables, we employed Fisher's exact test to ascertain the presence of nonrandom associations between variables and survival outcomes. Furthermore, logistic regression modeling was utilized to identify factors associated with categorical outcomes, such as the occurrence of immune-related adverse events (irAEs). All statistical analyses were conducted using JMP Pro 16 (SAS Institute Inc., Cary, NC), with statisti-

Table 1. Baseline Characteristics of the Study Population

Baseline characteristics	Distribution
Age of diagnosis	62 years (33 - 87)
Gender (male)	84%
Race	Caucasian: 88%, AA: 5%, Asian: 1%, other: 6%
Primary tumor type, esophageal vs. gastric	Esophageal: 61% (n = 39), gastric: 39% (n = 25)
Agent	Nivolumab: 42%, pembrolizumab: 58%
Line of ICI, > 2 lines vs. 1 - 2 lines	1 - 2: 73%, > 2: 27%
History of surgery	23%
History of radiation	41%
Chemotherapy combination	11% (FOLFOX: n = 4, and FOLFOX + trastuzumab: n = 2)
Lung metastasis-present	23%
Liver metastasis-present	44%
Bone metastasis-present	22%
Distant lymph node metastasis-present	50%
Other metastatic sites	33%
White blood cell count (baseline)	7.46
Red blood cell count	3.75
Hemoglobin (baseline)	10.73
Platelet count (baseline)	225.79
Neutrophil count (baseline)	6.71
Lymphocyte count (baseline)	0.93
Platelet to lymphocyte ratio	336.55
Neutrophil to lymphocyte ratio	12.14
Total bilirubin (baseline)	0.68
Albumin (baseline)	3.40
Alkaline phosphatase (baseline)	162.74
Aspartate transferase (baseline)	24.00
Thyroid stimulating hormone (baseline)	24.77
T4 (baseline)	30.60
HER2 status	4.37
Immune-related adverse event	Positive: 14%, negative: 69%, not available: 17%
Programmed cell death ligand 1(PD-L1) status	Yes: 8%
	Negative: 8%, 1 - 5: 28%, > 5: 25%, not available: 39%
Microsatellite instability-high	11%

AA: African American; ICI: immune checkpoint inhibitor; HER2: human epidermal growth factor receptor 2; FOLFOX: combination of 5-flurouracil and oxaliplatin.

cal significance set at $P < 0.05$.

Results

Baseline characteristics

We had 64 patients for analysis. Most of them were esophageal (39/64, 61%) primary tumors. Among the esophageal tumors, 34 cases were from lower esophageal and gastroesophageal junction tumors, and the rest were in the middle one-third of the esophagus. All of them were advanced tumors (four recurrent and 60 with distant metastases). At the time of analysis (median follow-up of 24 months), five patients were alive (three patients are on surveillance after 2 years of therapy). The rest of the baseline features are in Table 1.

Univariate analysis (UVA) and multivariate analysis (MVA) analysis

The group's PFS was 3 months, with a 95% CIs range between 2 and 4 months. The ICI-related overall survival (OS-ICI) and

Table 2. Multivariate Analysis of the Study Population

Source	Survival[a]					
	PFS		OS-ICI		OS	
	P value	HR	P value	HR	P value	HR
Gender, male vs. female	0.0274	0.132327	0.1238		0.0072	0.043668
Race	0.6482		0.4371		0.4106	
Primary tumor type, esophageal vs. gastric	0.499		0.8346		0.2608	
Line of ICI, > 2 lines vs. 1 - 2 lines	0.0259	0.176569	0.0404	0.160335	0.0003	0.02733
History of surgery	0.9153		0.8765		0.006	0.119958
History of radiation	0.9914		0.5511		0.2714	
Chemotherapy combination, yes vs. no	0.0071	0.08406	0.0514	0.706241	0.8084	
Lung metastases, yes vs. no	0.0682	5.051652	0.2754		0.0613	0.971694
Liver metastases, yes vs. no	0.4401		0.8525		0.9595	
Bone metastases, yes vs. no	0.3596		0.0305	3.633746	0.0009	10.98695
Distant lymph node metastases, yes vs. no	0.074	2.414344	0.3901		0.3246	
Other organs with metastases, yes vs. no	0.562		0.6469		0.0848	
White blood cell count (baseline)	0.6029		0.2715		0.1165	
Red blood cell count (baseline)	0.0206	5.792107	0.0373	5.556215	0.0202	1.202369
Hemoglobin (baseline)	0.6823		0.2597		0.0332	6.718667
Platelet count (baseline)	0.1289		0.7293		0.4175	
Neutrophil count (baseline)	0.1697		0.2122		0.7309	
Lymphocyte count (baseline)	0.0285	0.273647	0.0817	0.374776	0.4688	
Total bilirubin (baseline)	0.3151		0.6339		0.5006	
Albumin (baseline)	0.1049		0.2023		0.7287	
Alkaline phosphatase (baseline)	0.0224	1.00661	0.448		0.8361	
Alanine transferase (baseline)	0.0072	1.123848	0.2477		0.4527	
Aspartate transferase (baseline)	0.0289	0.897763	0.4947		0.5988	
Thyroid stimulating hormone (baseline)	0.0443	1.124609	0.2159		0.013	1.179802
T4 (baseline)	0.6535		0.4648		0.8827	
HER2	0.0061	0.563667	0.0525	0.096411	0.835	
Immune-related adverse event, yes vs. no	0.1034		0.0813	0.192533	0.114	
PD-L1, negative vs. > 1 vs. unavailable	0.0465	0.395261	0.3545		0.3955	
Microsatellite instability-high, yes vs. no	0.5449		0.9917		0.5808	

[a]Hazard ratios of the factors with insignificant (P > 0.05) were not mentioned. HR: hazard ratio; ICI: immune checkpoint inhibitor; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; OS: overall survival; OS-ICI: ICI-related overall survival.

OS were 5 months (range: 2 - 8 months) and 24 months (range: 14 - 38.5 months), respectively. The UVA results for the association with PFS, OS-ICI, and OS are presented in Tables 2 and 3 (Supplementary Material 1, gr.elmerpub.com). The UVA revealed that factors affecting PFS included primary tumor (gastric > esophageal; P value = 0.01), line of therapy (1 - 2 > 2; P value = 0.004), history of radiation therapy (XRT; no > yes; P value = 0.007), and chemotherapy combinations (CT-CC; yes > no; P value = 0.01). The factors affecting OS-ICI were line of therapy (P value = 0.02), XRT (P value = 0.04), and CT-CC (P value = 0.02). The OS-associated factors were the incidence of bone metastases (P value = 0.04) and PD-L1 status (P value = 0.005). Further details are provided here (Supplementary Material 1, gr.elmerpub.com).

The results of the multivariable Cox regression analysis (summarized in Table 3 and details in Supplementary Materials 2-4, gr.elmerpub.com) indicated that a shorter PFS was associated with an increased risk of lung metastases (adjusted hazard ratio (aHR): 5.05, 95% CI: 0.88 - 28.80), and a higher incidence of distant lymph node metastases (aHR: the results indicated that there was a 2.41-fold increased risk of death (95% CI: 0.92 - 6.35)), and a 56% decreased risk of death

Table 3. Summary of Multivariate Analysis of the Study Population

Outcome measured	Negative effect (hazard ratio > 1)	Positive affect (hazard ratio < 1)
Progression-free survival	HER2 positivity	Male gender
	Baseline RBC count, ALP, ALT, TSH	When used in the third line or more
		Used in combination with chemotherapy
		PD-L1 positive
		Baseline lymphocyte count and AST
ICI-related overall survival (OS-ICI)	Bone metastasis	When used in the third line or more
	Baseline RBC count	Baseline AST
Overall survival (OS)	Bone metastasis	Male gender
	Baseline RBC count, hemoglobin, and TSH levels	When used in the third line or more
		History of surgery

RBC: red blood cell; ALP: alkaline phosphatase; ALT: alanine transferase; TSH: thyroid-stimulating hormone, PD-L1: programmed cell death ligand 1; AST: aspartate transferase; ICI: immune checkpoint inhibitor; HER2: human epidermal growth factor receptor 2.

(95% CI: 0.12 - 2.63) associated with lower HER2 expression. Conversely, OS-ICI was significantly associated with chemotherapy combination (aHR: 0.71, 95% CI: 0.23 - 2.22), lower lymphocyte count baseline (aHR: 0.37, 95% CI: 0.12 - 1.09). Furthermore, the analysis revealed that there was a significant association between OS-ICI with HER2 and irAEs (aHR: 0.19, 95% CI: 0.03 - 1.23). Finally, a higher RBC count level was significantly associated with a shorter OS (aHR: 1.2, 95% CI: 0.94 - 1.51).

Comparing the responders and survivors

We divided the patients into good and bad responders or survivors to compare the differences in clinicopathological features associated with outcomes using median survival (PFS, OS-ICI, and OS). We further identified poor responders or survivors using a lower 95% survival cut-off. Results are summarized in Table 4, while details are provided here (Supplementary Materials 5-7, gr.elmerpub.com). In the supplementary materials, we did not give P values or details of insignificant features.

Responders: bad vs. good and poor vs. good

We had 39/64 patients in the bad responder's group (PFS $\leq$ 3 months) and 30/64 in the poor responder's group (PFS $\leq$ 2 months). We have nine patients with PFS between 2 to 3 months. The primary tumor, line, prior radiation, and chemotherapy combination are key, significantly different clinical

Table 4. Summary of Comparison of Various Groups in the Study Population

	Higher	Lower
Bad responders	Esophageal cancers	Chemotherapy combinations
	ICI use in the third line or more	Albumin
	History of radiation	
	Baseline total bilirubin and ALP	
Poor responders	ICI use in the third line or more	
	Baseline WBC, total bilirubin, ALP, and TSH	
Bad ICI-related overall survival (OS-ICI)	History of radiation	Chemotherapy combinations
	Baseline WBC count, total bilirubin, ALP, and TSH	Albumin
Poor ICI-related overall survival (OS-ICI)	History of radiation	Chemotherapy combinations
	Baseline WBC count, total bilirubin, ALP, AST, and TSH	Albumin
Bad overall survivors	Higher WBC count	History of surgery
Poor overall survivors	ICI use in the third line or more	History of surgery
	Liver metastasis	PD-L1 positive tumors
	Baseline WBC, platelet, and lymphocyte count	

ICI: immune checkpoint inhibitor; ALP: alkaline phosphatase; TSH: thyroid-stimulating hormone, PD-L1: programmed cell death ligand 1; AST: aspartate transferase; WBC: white blood cell.

features (Table 4). Baseline WBC counts, liver (TBil and albumin), and thyroid activity seem to impact the response.

ICI-related survival: bad vs. good and poor vs. good survivors

We had 34/64 patients in the bad survival group (OS-IC ≤ 5 months) and 24/64 in the poor survival group (OS-ICI ≤ 2 months). The differences were similar to the ones in the responders' comparison (Table 3).

OS: bad vs. good and poor vs. good survivors

We had 32/64 patients in the bad survival group (OS ≤ 24 months) and 17/64 in the poor survival group (OS ≤ 14 months). Bone and liver metastases, incidence of irAE, and PD-L1 were more unique to this comparison than the previous ones (Table 3).

Mean change in the hematological parameters associated with progression

We compared the mean change in the hematological parameters to identify any trend associated with progression in patients with documented progression (n = 61). A slight increase in the WBC count (by 1.54, P = 0.02) and a drop in lymphocyte count (by 0.1907, P = 0.003) were significant (Supplementary Material 8, gr.elmerpub.com). The drop in RBC counts and platelet-to-lymphocyte ratio (PLR) and the rise in hemoglobin level, platelets, ANC, and neutrophil-to-lymphocyte ratio (NLR) were insignificant (P > 0.05).

irAEs

We had five patients with irAEs (one pneumonitis, one dermatitis, one hypophysitis, one colitis, one colitis, and nephritis). Median ICI dose before irAE incidence was 2 (range: 1 - 7), and four patients (4/5) required hospitalization. Three (3/5) patients died from irAE, while two recovered (colitis and dermatitis) and restarted ICI. The mean changes in the blood count at irAE incidence were not significantly different before the first dose of ICI, but the difference in rise in ANC (by 5.29, P = 0.07), NLR (9.4, P = 0.09), and WBC (5.1, P = 0.09) had a trend toward significance. The rise in RBC (by 0.05) and platelets (by 2.6) and drop in hemoglobin (by 0.02) and lymphocyte counts (by 0.5) were not significant. We did not find any significant factors associated with the incidence of irAE.

Discussion

ICI is currently an integral part of advanced UGI cancer management with chemotherapy and HER2-directed therapy in eligible patients. Recently, it has been approved for early-stage esophageal after chemoradiation and surgery in select patients (with residual disease and R0 resection [13]. As discussed above, we do not have ideal biomarkers for patient selection and rely on IHC-based tests.

Multiple studies are underway to identify novel biomarkers to predict and monitor response to ICI, ranging from simple immunochemistry-based tests to complex spatial transcriptomics [14-17]. These approaches require limited and costly resources and may take years to trickle into clinical practice. Risk-stratifying patients based on baseline characteristics is a crude but simple way to identify a patient population that benefits from ICI. This understanding will facilitate the design of clinical trials that utilize ICI even after the failure of current first-line chemotherapy-ICI combinations. Moreover, it will help elucidate resistance mechanisms, laying the groundwork for future therapeutic strategies. Our comprehensive multivariate models incorporate real-world factors available in community practices, including instances where PD-L1 or HER2 status is unavailable. Some risk factors influencing our reported outcomes are easily explainable, such as PD-L1 CPS score. The futility of treating PD-L1-negative patients with ICI is echoed in our study too [18, 19]. Most of the patients in our population received ICI in the third or more line. Patients with performance status good enough to get ICI post-chemotherapy had good outcomes, which is not surprising. Alternatively, patients (all PD-L1 positive) with SOC chemotherapy-ICI (two got trastuzumab also) did better. A meta-analysis conducted last year demonstrated that combination therapy offers a clear advantage over chemotherapy alone, particularly in PD-L1-positive tumors [19]. It gives hope for planning future trials to use ICI alone or in combination with other targeted therapies if patients cannot tolerate FOLFOX or progress on it. However, there were too few HER2-positive tumors to make substantial conclusions. We must wait for real-world data to confirm the clinical benefit of chemotherapy, trastuzumab, and the ICI combination.

In our study, MVA yielded some notable findings, particularly regarding how baseline clinical characteristics (prior to ICI treatment) influenced OS. It was unsurprising that patients experiencing recurrence after definitive surgery had improved OS. Additionally, our findings highlighted a gender-based differential response to ICI, favoring males, which aligns with previous studies [20-22]. Patients receiving a single-agent ICI as a third-line or later treatment likely represent those with UGI cancers exhibiting less aggressive biology. While earlier studies suggested a poor response to ICI in patients with bone metastasis, the underlying mechanism remains unclear [23]. We hypothesize that it may disrupt the immune-related mechanisms involved in ICI activity, such as WBC or lymphocyte function and interferon signaling. ALP has been reported as a prognostic marker in liver, kidney, and lung cancers, with some studies indicating that elevated pretreatment levels could be related to bone metastasis or underlying liver diseases [24-26]. Further research is needed to confirm these findings in the context of esophageal cancers. Patterns influencing PFS generally mirrored those affecting OS, with a few differences. Notably, HER2-positive patients treated with ICI had poor PFS, although only one patient in this study received the typical KeyNote 811 regimen [2]. Our

patients underwent chemotherapy and nivolumab combination therapy, while the remaining 39 patients were treated with single-agent ICI in the third line or beyond. This confounding factor may not apply to current SOC where combination of chemotherapy, trastuzumab, and ICI is used in PD-L1-positive patients. Patients receiving ICI combined with chemotherapy demonstrated better PFS, consistent with findings from other studies [1].

The correlation between blood counts and outcomes in ICI-treated tumors is not new [27-35]. Multiple retrospective and clinical trials have shown it in different tumor types. Our study notes an interesting theme: poor outcomes associated with red blood components (RBC and hemoglobin), and good outcomes with lymphocyte counts. Complex blood cell signatures that include specific lymphocytes (such as interferons, natural killer cells, and $CD8^+$) may be more accurate, but as we discussed in above, it may take time to come into clinical practice [36]. Monitoring blood counts, especially lymphocytes, was associated with outcome prediction in ICI-treated cancers [34, 38]. The rise in WBC and drop in lymphocyte counts were significant in disease progression in our study, but the quantum of change in our study is too small to make substantial conclusions. The association with irAEs and blood counts in our study needs to be validated in earlier studies, but some studies (our own) broached this topic. The correlation between baseline thyroid function tests is not clear, but outcome association with the development of thyroid dysfunction after initiating ICI in various cancers was not consistent across the studies [38-43].

Comparison of the bad/poor responders or survivors with their respective good groups confirmed that they were in line with MVA results. Certain lab values, such as bilirubin, were on the higher end of the normal range, which is difficult to track and use in the clinic. We need multi-institutional collaborations to study the risk factors and biomarkers associated with irAE. Our study highlights the importance of closely monitoring high-risk patients, such as those with bone metastases, HER2-positive status, and abnormal baseline levels of thyroid-stimulating hormone (TSH), RBC, hemoglobin, and liver enzymes, for early signs of disease progression while on ICI therapy. It is crucial for treating physicians to be prepared with alternative strategies, including the possibility of enrolling patients in clinical trials (when available) and scheduling more frequent restaging scans. The study also underscores the necessity of conducting fundamental tests for PD-L1 and HER2 in all patients with UGI adenocarcinoma and recommends considering ICI-based combinations as a first-line treatment for eligible patients. Looking ahead, future trials in UGI cancers should aim to personalize treatment by factoring in clinical, pathological, and genomic features beyond just PD-L1 and HER2 status in the first-line setting.

The study's primary limitations include the small sample size (n = 64) and the heterogeneity in treatments received, such as the use of ICI in combination with chemotherapy or HER2 inhibitors versus as a single agent, as well as differences in prior management. However, by including only adenocarcinomas, we were able to reduce variability related to the primary tumor location, as the patients had tumors situated in the middle and lower thirds of the esophagus, the gastroesophageal junction, or the stomach. In our MVA, we accounted for this by using the distinction between gastric and esophageal tumors as a variable. This retrospective study restricted our ability to control baseline parameters (such as missing PD-L1 or HER2 data) and factors during follow-up, and we did not have a control group to provide definitive conclusions. The study period coincided with the transition to ICI-chemotherapy combination therapy as the SOC for advanced tumors, which means our findings might not fully reflect current management practices, as most patients received monotherapy in second or later lines of treatment. When interpreting the results, it is important to consider several confounding factors, such as the impact of surgery (in cases of recurrent versus initially advanced tumors), the role of XRT (palliative versus definitive or neoadjuvant), baseline performance status (which was not available), and genomic factors beyond PD-L1, HER2, tumor mutational burden, and MSI status.

In summary, we present baseline characteristics that help predict treatment response in UGI tumors treated with ICI. Multiple retrospective studies showed their reliability in various tumor types; however, factoring them along with baseline tumor characteristics gives a new perspective on managing UGI tumors. We need large prospective real-world UGI-specific studies to confirm them and develop effective treatment strategies to improve the outcomes and reduce irAEs in this population.

Supplementary Material

Suppl 1. Univariate analysis for progression-free survival and overall survival.

Suppl 2. Multivariate analysis for progression-free survival.

Suppl 3. Multivariate analysis for overall survival - immune-checkpoint inhibitor.

Suppl 4. Multivariate analysis for overall survival.

Suppl 5. Progression-free survival comparison.

Suppl 6. Overall survival - immune-checkpoint inhibitor comparison.

Suppl 7. Overall survival comparison.

Suppl 8. Mean change in blood counts.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Author Contributions

Conceptualization, methodology, and writing - original draft preparation: Ashish Manne. Biostatistics: Fode Tounkara and Ashish Manne. Data curation: Eric Min, Paul Samuel, Katherine Benson. Writing - review and editing: Anne M. Noonan, Arjun Mittra, John Hays, Sameek Roychowdhury, Pannaga Malalur, Shafia Rahman, Ning Jin, Kenneth Pitter, Eric Miller, Alexandra Diaz, Eric Min, Paul Samuel, and Katherine Benson. Supervision, Kai He.

Data Availability

The data presented in this study are available on request from the corresponding author for ethical reasons.

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