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Laboratory Indicators in Urinary Bladder and Renal Cell Cancer Patients Treated With Immune-Oncological Drugs.

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ABSTRACT:

Background: Urinary bladder (UB) and Renal Cell Carcinoma (RCC) are common in men than women with poor outcome. The novel immunotherapy (IT) drugs like Immune Check Point Inhibitors (ICIs) are effective but expensive. However, a cost-effective and reliable biomarker to predict response and clinical outcomes is lacking.Objective: To study the association of biochemical parameters, histopathological type, grades, number of immunotherapy cycles and demographic factors (age and gender) with Progression Free Survival (PFS) and Overall Survival (OS) in urinary bladder and renal cell Carcinoma patients treated with immune check point inhibitors. Method: It is a retrospective analysis. We included 52 patients with Urinary bladder and Renal Cell Carcinoma treated with immune check point inhibitors and the patients registered at Tata memorial cente from Jan 2008 to Dec 2019. Clinical evaluation and laboratory investigations were performed as a part of standard protocol. Laboratory parameters like Albumin(A), Globulin(G), Albumin Globulin Ratio(AGR), Histopathological Report (HPR) and tumour grade(low and high) of the Urinary bladder and Renal Cell Carcinoma were studied at the time of Tata Memorial Centre enrolment (TMH Enrol) and before the start (pre-treatment) of the immune check point inhibitors therapy. Results: Amongst the biochemical parameters, the pre-treatment Albumin Globulin Ratio was significantly associated with overall survival of the disease with p-value 0.035; hazard ratio 2.196 (95% CI – 1.057- 4.564). The progression free survival was not significant with p-value 0.093; hazard ratio 1.867 (95% CI – 0.901-3.869) in the pre- treatment Albumin Globulin Ratio.The median-based cut off for Albumin Globulin Ratio at pre- immune check point inhibitors therapy was found to be 1.1 (IQR 0.9-1.3) to differentiate between progressed and non-progressed cases with 53.3% sensitivity and 55.6% specificity and for overall survival, the sensitivity and specificity was 56.7% and 61.1% respectively.When demographic parameters like age and gender was analysed, there was no significant association with progression free survival and overall survival of disease. Also the progression free survival and overall survival of disease were not significant in histopathology type (Urinary bladder and Renal Cell Carcinoma) and tumour grade (low and high). The number of immunotherapy cycles were significantly associated with progression free survival with p = 0.029: hazard ratio 0.457 (95.0% CI 0.226 - 0.921) but not with overall survival of the disease. Conclusion: Simple, routinely available and cost effective Albumin Globulin Ratio from biochemical test has a great potential to be used as a biomarker to predict the overall survival in patients with urinary bladder cancer and Renal Cell Carcinoma patients treated with immune check point inhibitors.

Keywords: Urinary bladder Cancer, Renal Cell Carcinoma, Immune Check point Inhibitors

1. Introduction

Genitourinary cancer deals with cancers of the urinary system of men and women and the reproductive organs in men. Urinary cancers are resulting from abnormal neoplastic growth of cells in the prostate, bladder, kidney, adrenal gland, urethra or other parts of the urinary tract system.

Urinary bladder cancer (BC) is one of the most prevalent urological cancers all around the world; with an increasing rate of morbidity and mortality (1). It is the 9th most commonly diagnosed cancer, and the 13th cause of cancer-related mortality worldwide (2). BC cancer begins when healthy most commonly urothelial cells in the bladder lining, change and grow out of control, forming a mass or tumour. Urothelial cells also line the renal pelvis and ureters. Malignant growth arising in the renal pelvis and ureters are also included in urothelial cancers which frequently called upper tract urothelial cancer and treated similar to bladder cancer.

Renal Cell Carcinoma (RCC), the most common and lethal malignant type of kidney tumour, accounts for about 2-3% of all malignant diseases in adults. Worldwide, there are over 400,000 new cases of RCC. Over 170,000 deaths occur annually due to kidney cancer (3). Clear cell RCC (ccRCC) is the most common subtype of RCC, accounting for approximately 70 - 80% of the cases (4).

Sex and gender disparities exist in all facets of healthcare and disease which can arise as a result of several factors, including social, behavioural, and biological determinants of health (5). Biological differences that drive health discrepancies can lead to altered clinical outcomes for male and female subjects. Therefore, it is pivotal to have a thorough understanding of the biological differences between men and women in order to develop more personalized preventative measures and treatment plans for different diseases.

BC is four times more common in men than women, with respective to occurrence of 9.6/100,000 among men and 2.4/100,000 among women worldwide (6). RCC is approximately two times more common in men compared to women (7). It can be aggressive and grow faster than other kidney cancers. Several studies have demonstrated sex-related differences in Bladder cancer oncologic outcomes. They are due to genetic, anatomic, hormonal, social and environmental factor differences that may be operational between males and females (8–10). However age is also an indicator used to assess prognosis in many solid cancers, especially in clear cell Renal Cell Carcinoma (ccRCC), and is an important risk factor (11, 12). However, we focused on age and gender disparities in bladder cancer and renal cell cancer patients treated with ICIs to identify any difference in survival outcome.

Bladder cancer cells can also be described as either low grade or high grade. Low grade BC cancer is less likely to grow, spread and come back after treatment. High grade BC cancer is more likely to grow, spread and come back after treatment (13-17).

Tumour stage is the key prognostic variable in renal cell carcinoma (RCC). The most accepted and widely used system for grading renal cell carcinoma (RCC) is a nuclear grading system described in 1982 by Fuhrman et al, which synchronously evaluates nuclear size and shape, and nucleolar prominence. However, disagreement and grading imprecision may occur among these three parameters, leading to the Fuhrman grading irrelevant. In 2012, the International Society of Urologic Pathologists (ISUP) proposed a novel, validated grading system for clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) which has been implemented by the World Health Organization (WHO) (18-21).

Inflammation is a distinctive characteristic of cancer that reflects the host's immune response to cancer cells. The compromised immune response essentially contributes to the development and progression of malignancies. In many cancer cases, there are increasing evidence for the role of dysregulated local and systemic immune responses in the progression of tumours and disease-free survival of patients. The knowledge of dysregulated immune responses and inflammatory reactions provides a prospect to study the biomarkers associated with these immune responses and inflammatory reactions and their usefulness to predict the clinical course of diseases and therapeutic responses.

Albumin and globulin are two major serum proteins that can indicate the systemic inflammatory response. Albumin regulates the systemic inflammatory reaction, as well as exerts antioxidant effects. It also plays an important role in stabilizing cell growth and DNA replication. A low level of albumin has been valuable prognostic tool for various cancers. Globulin increases with the accumulation of acute-phase proteins and immunoglobulins, which indicate an immunologic and inflammatory state. Thus these two proteins play an important role in immunity and inflammation. Low albumin levels can decrease the response to treatment in cancer patients, and its clinical role as an adverse prognostic biomarker was also reported in various human malignancies. Albumin-to-globulin ratio (AGR) is also reported to be a potential prognostic biomarker in several cancers (22, 23). Considering increase in morbidity and mortality, it is apparent that search for independent, low-cost, standardized, reliable and reproducible prognostic biomarkers are needed.

Immune checkpoint inhibitors (ICIs) have reported incomparable results in the treatment of BC and RCC patients, as monotherapy or in combination with other anticancer agents. However, very little information is available regarding the association between different clinic-pathological features and survival in this setting.

The recent findings of immune checkpoint inhibitors (ICIs) such as Programmed cell Death 1(PD-1) inhibitors, Cytotoxic T- Lymphocyte – associated Antigen 4(CTLA4) inhibitors, etc., has transformed the therapeutic dynamics in many solid tumour cancers with poor clinical outcomes including genitourinary cancer. However, these novel immunotherapy drugs are very expensive and hence less economical in low and middle-income countries like India. Moreover, data shows that these novel immunotherapy drugs are not effective in a subset of patients. Hence, it is more relevant to use these expensive therapies in selective patients who will benefit from such therapies. Unfortunately, no routinely available biomarker can be used to evaluate the effectiveness of these ICIs in patients with Urinary bladder (UB) and Renal Cell Cancer (RCC).

Therefore, there is a grave need to identify routinely used cost-effective, reliable, reproducible biomarkers to predict therapeutic response and clinical outcomes in patients with genitourinary cancers treated with ICIs. Furthermore, a universal prognostic factor that can predict survival regardless of the type of cancer will help to simplify the management of cancer patients.

Thus, in this study, we aimed to investigate the clinical utility of laboratory biomarkers and analyse the association of biochemical parameters, histopathological grades, number of immunotherapy cycles and demographic factors with progression free survival (PFS) and overall survival (OS) in UB and RCC patients treated with ICIs.

2. Material and Methods

This is a retrospective study. The patients of urinary bladder and RCC, who were enrolled at TMC from Jan 2008 to Dec 2019 were included. Amongst these 52 patients of urinary bladder and

RCC, the first treatment with ICIs started from November 2016 though the first patient was registered at TMC in Jan 2008.

Clinical evaluation and laboratory investigations were performed as a part of standard protocol. All patients had biochemical test collected on the date of TMC enrollement and within 7 days before start of immunotherapy. Amongst the biochemical parameters Albumin(A), Globulin(G), AlbuminGlobulin Ratio(AGR) were studied at the time of TMH enrolment (TMH Enrol) and pre-treatment (before the start) of the ICIs therapy (IT). Histopathology report(HPR) obtained from surgical pathology. Low grade was considered as geade 1 and 2 where as high grade was cosidered as grade 3 and grade 4 for urinary bladder cancer as well as for RCC grade based on Fuhrman grading and ISUP grading .
Patient's demographic data (age, gender), treatment history (immunotherapy cycles), and laboratory data were obtained from Electronic Medical Record (EMR) of Tata Memorial Centre (TMC).
The combination of two immune checkpoint inhibitors - ipilimumab (Yervoy) and nivolumab (Opdivo) - has been approved for the treatment of advanced kidney cancer in first line therapy. Two combinations of targeted therapy plus an ICI have been approved for people with advanced kidney cancer in first line therapy.

- Pembrolizumab (Keytruda), plus the targeted drug axitinib (Inlyta)
- Pembrolizumab plus lenvatinib
- Nivolumab plus cabozantinib

In second line therapy single agent immunotherapy (Nivolumab) has been used.
For patients with urinary bladder cancer, Pembrolizumab or Nivolumab or Atezolizumab were used either in first line or second line therapy.

Inclusion Criteria:
• Patients diagnosed with urinary bladder and kidney cancer in TMC from Jan 2008 to Dec 2019 and treated in adult medical oncology.
• Patients treated with ICIs in TMC between 2008 to Dec 2019.
• Patients treated during palliative intent ICIs either in first/ second line therapy of their course.

Exclusion criteria:
• Patients with inadequate clinical/demographical data available in TMC EMR.
• Patients receiving ICIs in adjuvant setting.
The TMC patients demographic were recorded at the time of TMC enrolment, histopathology report and grading done after the biopsy at TMC or slides were reviewed at the time of TMC enrolment. Biochemistry laboratory had received the whole blood samples for biochemical test at the time of TMH enrolment (TMH Enrol) and pre-treatment (before the start) of the ICIs therapy (IT). The biochemical parameters were analysed using automated biochemical analysers Au5800 and Cobos6000. The start of immunotherapy drugs and number of immunotherapy cycles were recorded from clinical evaluation from EMR.

Statistical analysis:
Descriptive statistics were used to summarize the data. Categorical data was summarized using counts and percentages. Continuous data is summarized using Median (IQR). The association between the HPR, grades with progression status were assessed using chi-square test.

The PFS and OS were estimated between the HPR groups, grades groups, age, gender, number of immunotherapy cycles (<6 and >6 cycles), AGR ratio categorized at 1.11 (median value) at TMH enrolment and before start of Immunotherapy using Kaplan- Meier method. Log-rank test was used to compare the survival between the AG ratio <1.11 and >=1.11. Cox Proportional hazards model was used to estimate the Hazard Ratio with 95% CI.

The median (IQR) and mean (SD) of albumin, globulin, AGR ratio were evaluated. Box-whisker plots were used to graphically represent the distribution of AGR ratio across progressed and non-progressed groups. A p-value less than 0.05 were considered as statistically significant. All statistical analysis was performed in IBM SPSS version 29.

Sample size:

Retrospectively patients diagnosed with urinary bladder and kidney cancer in TMC enrolled from Jan 2008 to Dec 2019 and treated with ICIs from November 2016 were included in the analysis.

3. Results

Within the cohort, tumour histology includes 26 (50%) urinary bladder cancers and 26 (50%) renal cell carcinoma cases treated with immunotherapy drugs. There sub classification of both the cancer cases was shown in Table (1) according to histopathology report (HPR). Amongst urinary bladder cancer patients, papillary urothelial carcinoma and high grade urothelial carcinoma cases were highest. Clear cell renal cell carcinoma patients were around 65% in renal cell cancer patients.

Patients had median age of 63 (IQR 58-72) years, 42(81%) were men and 10(19%) were women. Amongst 52 patients, the median immunotherapy cycles were 12 (IQR 6-16). The disease progression of urinary bladder and RCC patients was based on radiology reports. Response was evaluated for 52 patients with computed tomography, positron emission tomography or magnetic resonance imaging, 34 (65%) patients were found to be with disease progression and 18(35%) patients had no disease progression Table (1).

GENDER	
Female	10(19%)
AGE	Median - 63 (IQR 58-72) Years
GRADE	
Low grade	12 (23%)
High grade	40 (77 %)
IMMUNOTHERAPY CYCLES	Median - 12 (IQR 6 -16) Cycles
RESPONSE	
Progression	34 (65.4%)
No progression	18 (34.6%)
HPR Type	
UB	26 (50%)
RCC	26 (50%)
Papillary urothelial carcinoma (9)	Clear cell renal cell carcinoma (17)

Poorly differentiated (1)	Metastatic renal cell carcinoma (3)
Solid urothelial carcinoma (3)	Collecting duct carcinoma (2)
Metastatic urothelial carcinoma (1)	Papillary renal cell carcinoma (3)
Papillary and solid urothelial carcinoma (3)	Conventional Renal cell carcinoma (1)
High grade urothelial carcinoma (9)	

Table (1): Demographic and sub classification of UB and RCC patients.

Albumin and globulin are two major serum proteins that can reflect the systemic inflammatory response in cancer patients. Therefore, amongst the biochemical parameters, these two parameters and their ratio were evaluated with progressed and non-progressed groups. Since the data of albumin, globulin and albumin globulin ratio (AGR) was not normally distributed, the median (IQR) was reported for progressed and non-progressed groups.

The median (IQR) for albumin were 3.7 (3.1 - 3.9) and 3.9 (3.5 - 4.3) at the time of TMC enrolment and the pre-treatment of the ICIs therapy (before start of IT) respectively for the non-progressed group. Similarly the median (IQR) for albumin were 3.7 (2.7 - 4) and 4 (3.8 - 4.3) at the time of TMC enrolment and the pre-treatment of the ICIs therapy (before start of IT) respectively for the progressed group.

The median (IQR) for globulin were 3.1 (2.6 - 3.9) and 3.5 (3.1 - 3.9) at the time of TMC enrolment and the pre-treatment of the ICIs therapy (before start of IT) respectively for the non-progressed group. Similarly the median (IQR) for globulin were 3.5 (3.1 - 4.6) and 3.6 (3.2 - 4.1) at the time of TMC enrolment and the pre- treatment of the ICIs therapy (before start of IT) respectively for the progressed group.
When AGR was evaluated, the median (IQR) for AGR were found to be 1.2 (0.8 - 1.4) and 1.1 (0.9 - 1.3) at the time of TMC enrolment and the pre-treatment of the ICIs therapy (before start of IT) respectively for the non-progressed group. Similarly the median (IQR) for AGR were 0.9 (0.8 - 1.1) and 1.1 (1 - 1.3) at the time of TMC enrolment and the pre-treatment of the ICIs therapy (before start of IT) respectively for the progressed group.
There was no significant difference between distribution of albumin; globulin and AGR at the time of TMC enrolment and the pre-treatment of the ICIs therapy (before start of IT) when compared with progressed and non-progressed group using Mann-Whitney U test Table (2).

PARAMETERS	NON PROGRESSED			PROGRESSED			p-value
	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)	
Albumin at TMC Enrolment	16	3.5 (3.7)	3.7 (3.1 - 3.9)	19	3.4 (3.7)	3.7 (2.7 - 4)	0.833
Globulin at TMC Enrolment	16	3.2 (3.1)	3.1 (2.6 - 3.9)	19	3.7 (3.5)	3.5 (3.1 - 4.6)	0.066
AGR at TMC Enrolment	16	1.1 (1.2)	1.2 (0.8 - 1.4)	19	1 (0.9)	0.9 (0.8 - 1.1)	0.117
Albumin before start of IT	18	3.8 (3.9)	3.9 (3.5 - 4.3)	30	3.9 (4)	4 (3.8 - 4.3)	0.461

Globulin before start of IT	18	3.6 (3.5)	3.5 (3.1 - 3.9)	30	3.6 (3.6)	3.6 (3.2 - 4.1)	0.579
AGR before start of IT	18	1.1 (1.1)	1.1 (0.9 - 1.3)	30	1.1 (1.1)	1.1 (1 - 1.3)	0.84

Table (2): The mean (SD), median (IQR) and p- value of biochemical parameters in the progressed and non-progress patients.

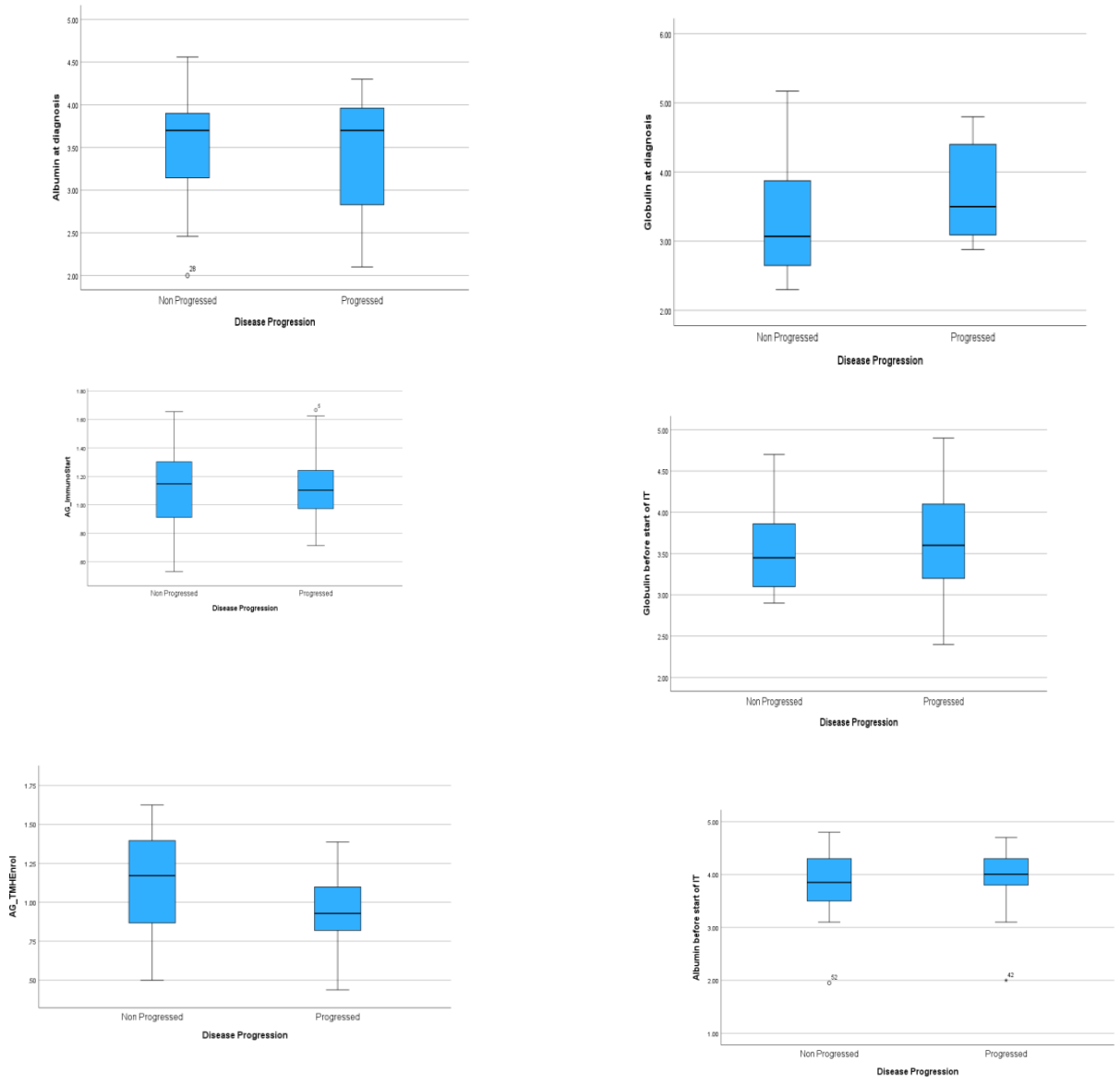


Figure (1): Boxplots representing the distribution of biochemical parameters among the progressed and non-progressed groups.

In males of 42 cases 27 were progressed with median PFS (mPFS) of 8.444 months (95% C.I. 4.506 - 12.381) whereas in females of 10 cases 7 were progressed with mPFS of 18.168 months (95% C.I. 0 - 39.528) indicating no significant difference in PFS between males and females with p = 0.66. Amongst the age group, the mPFS in <63 years was 9.561 (95% C.I. 0.41- 18.711) and in >63 years was 7.622 (95% C.I. 3.855 - 11.389) show no significant difference with p = 0.635.
However in 40 cases with high grade tumour stage, 28 were progressed with mPFS of 8.674 months (95% C.I. 1.307 - 16.04) as compared to 12 low grade tumour stage, 6 cases progressed with mPFS of 9.561 months (95% C.I. 0 - 58.947) indicating no significant difference in PFS between the grades with p value 0.526. Histopathological diagnosed 26 cases of urinary bladder cancer 20 progressed cases showed mPFS of 8.444 months (95% C.I. 0 - 17.104) whereas 14 out of 26 RCC cases showed mPFS of 9.561months (95% C.I. 0 - 31.346) indicating no significant difference in histopathology category with p= 0.462.
In the cohort, mPFS in number of immunotherapy cycles <=6 is 2.234 (95% C.I. 0.989- 3.479) and in number of immunotherapy cycles >6 is 15.901 (95% C.I. 6.983- 24.819) showed significant difference with p value 0.025.
The comparison of AGR at the time of TMH enrolment categorized at <=1.11 showed mPFS of 8.674 months (95% C.I. 0 - 18.01) whereas AGR >=1.11 showed mPFS of 15.901 months (95% C.I. 11.521 - 20.282) indicating no significant difference with p value 0.151. On the other hand, the comparison of AGR before the start of immunotherapy categorized at <=1.11 showed mPFS of 7.622 months (95% C.I. 0.579 - 14.665) whereas AGR >=1.11 showed mPFS of 18.366 months (95% C.I. 5.929 - 30.802) indicating closer to significance with p value 0.088 Table (3) Figure (2). The results of PFS and OS estimates were obtained using Kaplan Meier (KM) method and compared between groups using log rank test in 52 cases (Table 3).

Progression Free Survival						
Category	Total No.	No. of Events	Median PFS in months	95% Confidence Interval		P
				Lower Bound	Upper Bound	
Overall	52	34	8.674	2.259	15.088	
Gender						
Male	42	27	8.444	4.506	12.381	0.66
Female	10	7	18.168	0	39.528	
Grade						
Low grade	12	6	9.561	0	58.947	0.526
High grade	40	28	8.674	1.307	16.04	
HPR						
UB	26	20	8.444	0	17.104	0.462
RCC	26	14	9.561	0	31.346	
No. of immunotherapy cycles						
<=6	17	14	2.234	0.989	3.479	**0.025**
>6	35	20	15.901	6.983	24.819	
Age						

<63	25	16	9.561	0.41	18.711	0.635
>=63	27	18	7.622	3.855	11.389	
Albumin Globulin Ratio (AGR)						
AGR at TMC Enrolment						
<=1.11	17	11	8.674	0	18.01	0.151
>=1.11	18	8	15.901	11.521	20.282	
AGR before start of IT						
<=1.11	24	16	7.622	0.579	14.665	0.088
>=1.11	24	14	18.366	5.929	30.802	

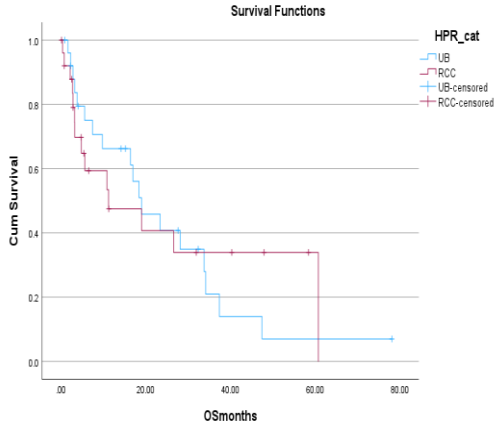
Table (3): Enlist the estimates, total number and events, of PFS such as Median PFS with 95% CI with p value for comparison of PFS between the categories of variables using Log rank test.

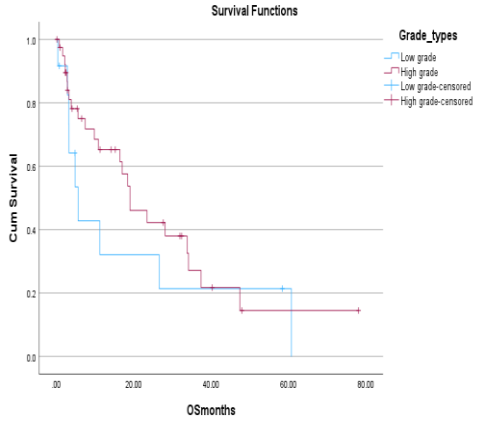
In 42 male patients, 25 deceased with median OS was 18.464 (95% CI 6.925 - 30.003) where as in 10 female cases, 7 deceased with median OS of 19.055 (with 95% CI 11.472 - 26.639) indicating no significant difference in survival between males and females with p = 0.966. When age groups categorized at <63 and >=63 showed no significant difference in median OS 19.055 (95% CI 2.797 - 35.313) and 18.464 (95% CI 14.573 - 22.355) respectively with p = 0.486.
The tumour grade categorized at low and high grade showed no significant difference in median OS 5.651(95% CI 2.259- 9.042) and 19.055 (95% CI 11.445- 26.666) respectively with p = 0.364. Similarly the urinary bladder cancer and RCC histological type showed no significant difference in median OS 19.055 (95% CI 10.099 - 28.012) and 11.269 (95% CI 0 - 27.251) respectively with p = 0.971.
The number of immunotherapy cycles categorized at. <=6 and >6 showed no significant difference in median OS 5.618 (95% CI 1.743 - 9.493) and 23.458 (95% CI 14.089 -32.826) respectively with p = 0.243.
The AGR values at the time of TMH enrolment categorized at <1.11 and >=1.11 showed no significant difference in median OS 10.908 (95% CI 3.022 - 18.793) and 23.458 (95% CI 9.725-37.19) respectively with p=0.728. The AGR values before start of immunotherapy categorized at <1.11 and >=1.11 showed significant difference in median OS 5.651 (95% CI 0-14.96) and 28.156 (95% CI 10.69-45.62) respectively with p = 0.030 Table (4) Figure (2).

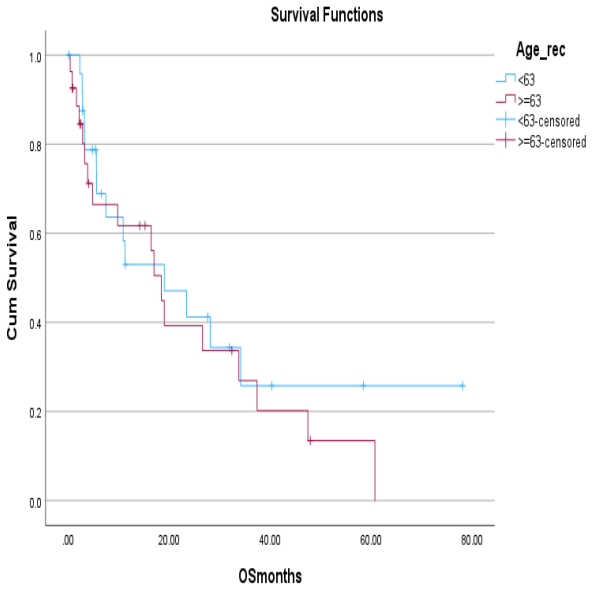
Overall Survival (OS)						
Category	Total No.	No. of Events	Median OS in Months	95% Confidence Interval		P
				Lower Bound	Upper Bound	
Overall	52	32	18.464	10.124	26.804	
Gender						
Male	42	25	18.464	6.925	30.003	0.966
Female	10	7	19.055	11.472	26.639	
Grade						

Low grade	12	9	5.651	2.259	9.042	0.364
High grade	40	23	19.055	11.445	26.666	
HPR						
Category	Total No.	No. of Events	Median OS in Months	95% Confidence Interval		P
				Lower Bound	Upper Bound	
UB	26	18	19.055	10.099	28.012	0.971
RCC	26	14	11.269	0	27.251	
No. of immunotherapy cycles						
<=6	17	10	5.618	1.743	9.493	0.243
>6	35	22	23.458	14.089	32.826	
Age						
<63	25	14	19.055	2.797	35.313	0.486
>=63	27	18	18.464	14.573	22.355	
Albumin Globulin Ratio (AGR)						
AGR at TMC Enrolment						
<=1.11	17	9	10.908	3.022	18.793	0.728
>=1.11	18	12	23.458	9.725	37.19	
AGR before start of IT						
<=1.11	24	17	5.651	0	14.962	**0.03**
>=1.11	24	13	28.156	10.694	45.619	

Table (4): Enlist the estimates, total no. and events, of OS such as Median OS with 95% CI with p value for comparison of OS between the categories of variables using Log rank test.



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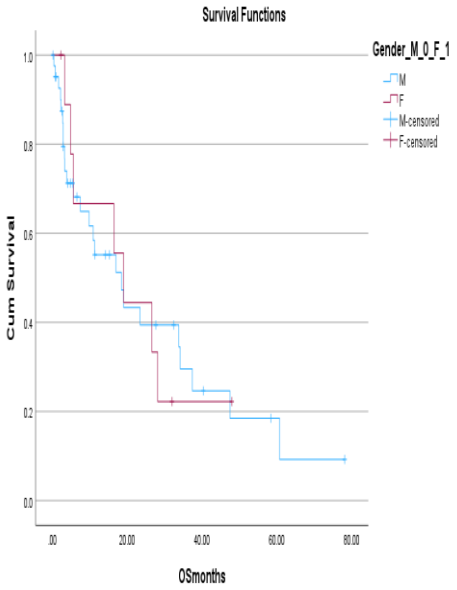
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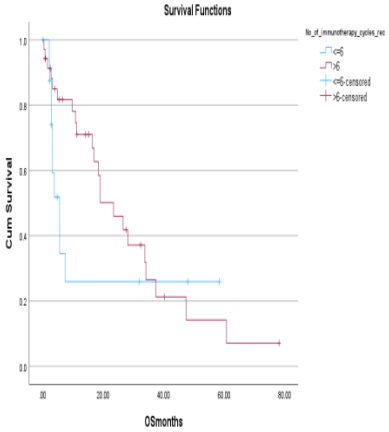
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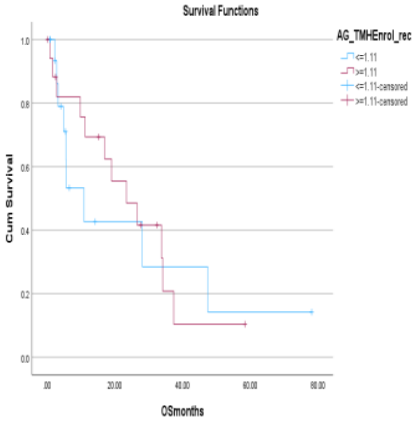
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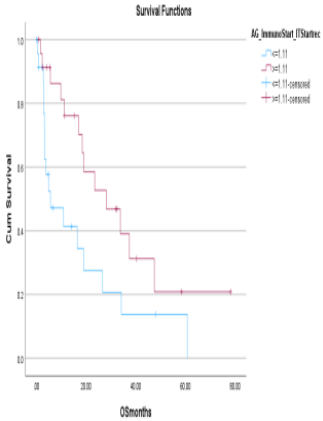
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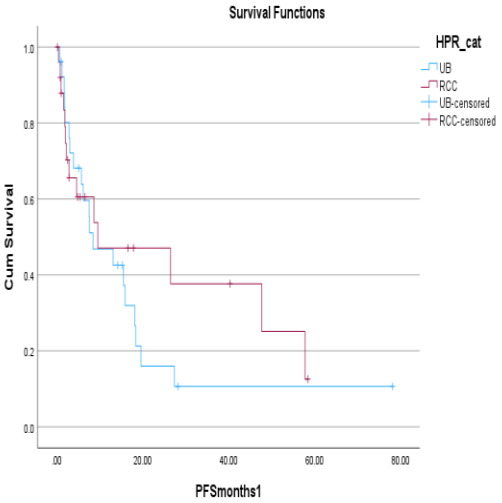
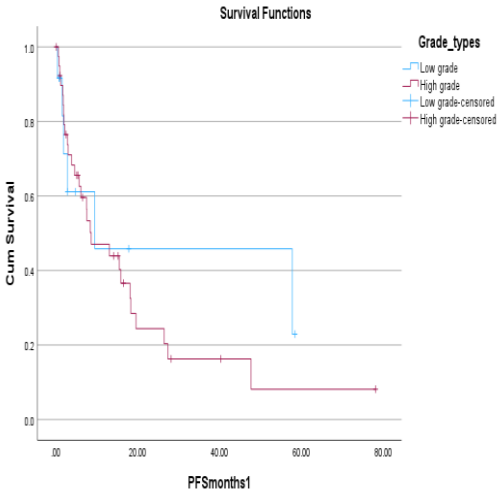
Cum Survival
OSmonths


Survival Functions
HPR_cat
UB
RCC
UB-censored
RCC-censored
Cum Survival
PFSmonths1


Survival Functions
Grade_types
Low grade
High grade
Low grade-censored
High grade-censored
Cum Survival
PFSmonths1

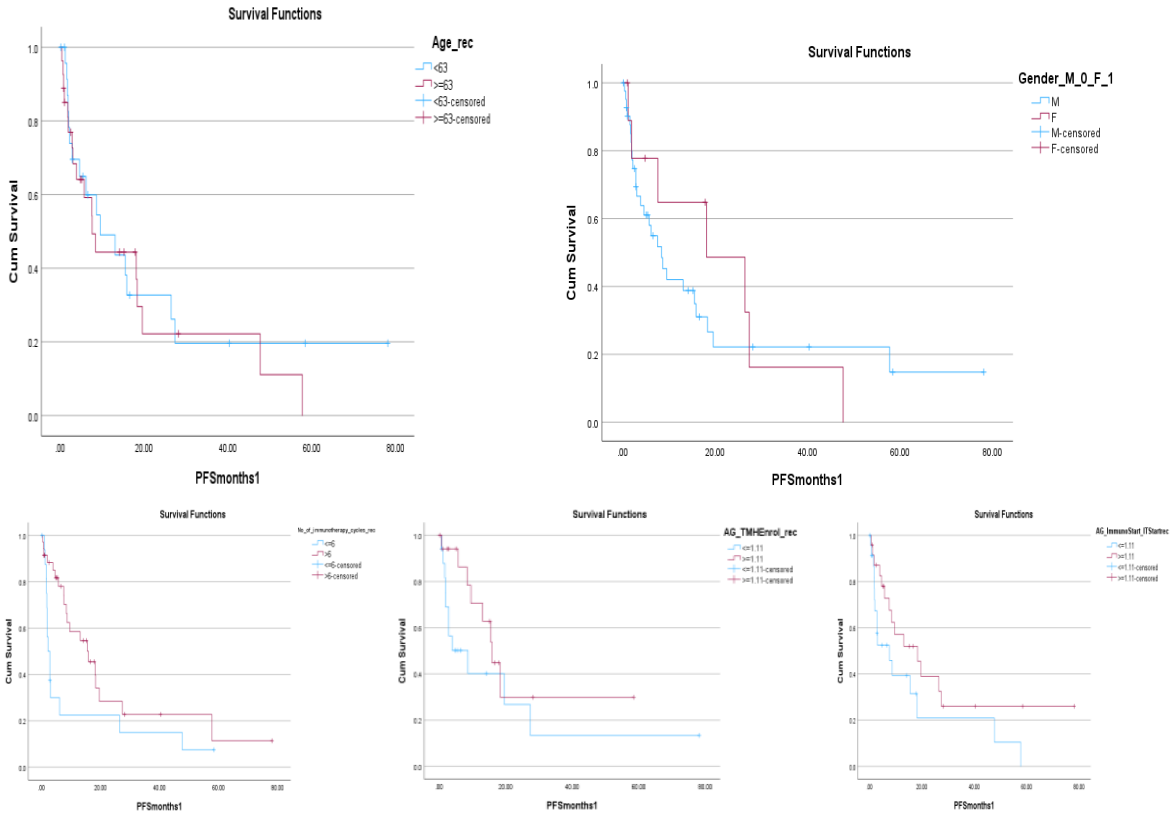


Figure (2): Enlisted the graphs with Kaplan Meier Curves for OS and PFS, Y axis indicate the Cumulative survival proportions and X axis indicates the PFS and OS duration in Months.

Subgroup	Variable	Category	N (Events)	HR	95% CI		P
OS for RCC	**AGR before start of IT**	>1.11	8 (2)	1			0.049
		<=1.11	16 (4)	**4.698**	1.010	21.856	
OS for UB	AGR before start of IT	>1.11	16 (11)	1			0.181
		<=1.11	8 (6)	2.050	0.716	5.869	
OS for RCC	AGR at TMC Enrolment	>1.11	7 (4)	1			0.108
		<=1.11	8(5)	6.256	0.670	58.421	
OS for UB	AGR at TMC Enrolment	>1.11	8 (5)	1			0.928
		<=1.11	12 (7)	0.945	0.282	3.172	
OS for RCC	No. of IT cycles	<=6 Cycles	10 (4)	1			0.640
		>6 Cycles	16 (10)	1.327	0.40	4.345	

					6		
OS for UB	**No. of IT cycles**	<=6 Cycles	7 (6)	1			0.002
		>6 Cycles	19 (12)	**0.030**	0.003	0.263	
PFS for RCC	AGR before start of IT	>1.11	8 (3)	1			0.131
		<=1.11	16 (9)	2.770	0.737	10.409	
PFS for UB	AGR before start of IT	>1.11	16 (11)	1			0.200
		<=1.11	8 (7)	1.954	0.702	5.441	
PFS for RCC	AGR at TMC Enrolment	>1.11	7 (1)	1			0.260
		<=1.11	8 (4)	114.004	0.030	infinite	
PFS for UB	AGR at TMC Enrolment	>1.11	8 (4)	1			0.290
		<=1.11	12 (10)	1.880	0.584	6.047	
PFS for RCC	No. of IT cycles	<=6 Cycles	10 (7)	1			0.449
		>6 Cycles	16 (7)	0.661	0.226	1.933	
PFS for UB	**No. of IT cycles**	<=6 Cycles	7 (7)	1			<0.001
		>6 Cycles	19 (13)	**0.066**	0.016	0.277	

Table (5): Indicates hazard ratios (HRs), confidence intervals (CIs), and associated p-values for different subgroups within the context of overall survival (OS) and progression-free survival (PFS) for renal cell carcinoma (RCC) and urinary bladder cancer (UB), based on various factors such as AGR levels and number of immunotherapy cycles. The hazards with >1 is considered as increased risk of developing the event of interest.

The estimate of HR for OS and PFS were compared between the AGR <=1.11 and >1.11 groups and no. of immunotherapy cycles in subgroups of RCC and UB patients.
In UB cohort, the HR for OS and PFS were 0.03 (95% CI 0.003 - 2.63) and 0.066 (95% CI 0.016 - 0.277) respectively showing decreased hazards in >6 cycles of immunotherapy than patients with <6 months of immunotherapy. In RCC cohort, HR for OS in AGR at start of IT in <=1.11 group was 4.69 (95% CI 1.01 - 21.856) with p = 0.049 showing significant increase in hazards as compared to patients with >1.11 AGR value.
The whole cohort (UB and RCC) was evaluated for hazard ratios (HRs), confidence intervals (CIs) and associated p-values, to compare the overall survival (OS) and progression-free survival

(PFS) with the AGR at the time of TMH enrolment and AGR before the start of IT and number of immunotherapy cycles using Kaplan Meier method.

It has been observed that the HR for OS in AGR at the time of TMC enrolment categorised at <=1.11 is 1.47 (0.61 - 3.572) with p value 0.386 as compared to the >1.11 group of cases. The HR for OS in AGR before the start of immunotherapy categorised at <=1.11 is 2.196 (95.0% CI 1.057 - 4.564) with p = 0.035 as compared to >1.11 group showing significant increase in hazards for death by 2.19 times. The HR for OS in number of immunotherapy cycles categorised at >6 Cycles was 0.636 (95.0% CI 0.295- 1.371) with p = 0.248 as compared to <=6 Cycles group of cases.

Similarly the HR for PFS in AGR at the time of TMH enrolment categorised at <=1.11 is 3.041 (95.0% CI 1.084 - 8.534) with p = 0.035 as compared to >1.11 group of cases showing significant increase in hazards for death by 3.04 times. The HR for PFS in AGR before the start of immunotherapy categorised at <=1.11 was 1.867 (95.0% CI 0.901- 3.869) with p = 0.093 as compared to >1.11 group of cases. The HR for PFS in number of immunotherapy cycles categorised at >6 Cycles was 0.457 (95.0% CI 0.226 - 0.921) with p = 0.029 as compared to <=6 Cycles group showing a significant increase in hazards for progression by 0.457 times Table (6).

Variable	Category	N (Event)	HR	95.0% CI for HR		P
OS						
AGR at TMC Enrolment	>1.11	20 (12)	1			0.386
	<=1.11	15 (9)	1.477	0.611	3.572	
AGR before start of IT	>1.11	24 (13)	1			**0.035**
	<=1.11	**24 (17)**	**2.196**	**1.057**	**4.564**	
No. of IT cycles	<=6 Cycles	17 (10)	1			0.248
	>6 Cycles	35 (22)	0.636	0.295	1.371	
PFS						
AGR at TMC Enrolment	>1.11	20 (14)	1			**0.035**
	<=1.11	**15 (5)**	**3.041**	**1.084**	**8.534**	
AGR before start of IT	>1.11	24 (14)	1			0.093
	<=1.11	24 (16)	1.867	0.901	3.869	
No. of IT cycles	<=6 Cycles	17 (14)	1			**0.029**
	>6 Cycles	**35 (20)**	**0.457**	**0.226**	**0.921**	

Table (6): Hazards for AGR categorized at >1.11, <=1.11 before the start of Immunotherapy and at the time of TMH enrolment and number of immunotherapy cycles for OS and PFS in whole cohort.

The median-based cut off for AGR at pre-ICI therapy was found to be 1.1 (IQR 0.9-1.3) to differentiate between progressed and non-progressed cases**.** The sensitivity of AGR values at the time of TMH enrolment categorized as <=1.11 and >1.11 showed 73.68 % (95% CI 48.80 - 90.85) an 62.50% (95% CI 35.43 - 84.80) specificity with Positive Predictive Value (PPV) of 70% (95% CI 53.99 - 82.27%), Negative Predictive Value (NPV) of 66.67% (95% CI 46.27 - 82.29%) and accuracy of 68.57 (95% CI 50.71 - 83.15%) showed a good diagnostic accuracy for detecting progression.

Similarly, the sensitivity for AGR before the start of immunotherapy were categorized as <=1.11 and >1.11 showed 53.33% (95% CI 34.33 - 71.66) and 55.56%, (95% CI 34.33 - 71.66) specificity with PPV of 66.67% (95% CI 51.94 - 78.73), NPV of 41.67% (95% CI 28.91 - 55.64) and accuracy of 54.17% (95% CI 39.17 - 68.63) showed a good diagnostic accuracy for detecting progression Table (7).

Category			**Disease Progression**		**Total**	**Statistic**	**Value**	**95% CI**
			Progressed	**Non Progressed**				
AGR at TMC Enrolment	<=1.11	Count	14	6	20			
		% within AGR at TMC Enrolment	70.00%	30.00%	100.00%	Sensitivity	73.68%	48.80 - 90.85
		% within Disease Progression	73.70%	37.50%	57.10%	Specificity	62.50%	35.43 - 84.80
	>1.11	Count	5	10	15	Positive Likelihood Ratio	1.96	0.99 - 3.91
		% within AGR at TMC Enrolment	33.30%	66.70%	100.00%	Negative Likelihood Ratio	0.42	0.18 - 0.98
		% within Disease Progression	26.30%	62.50%	42.90%	Disease prevalence (*)	54.29%	36.65 - 71.17
	Total	Count	19	16	35	Positive Predictive Value (*)	70.00%	53.99 - 82.27
		% within AGR at TMC	54.30%	45.70%	100.00%	Negative Predictive Value (*)	66.67%	46.27 - 82.29

		Enrolment						
		% within Disease Progression	100.00%	100.00%	100.00%	Accuracy (*)	68.57%	50.71 - 83.15
AGR before start of IT	<=1.11	Count	16	8	24			
		% within AGR before start of IT	66.70%	33.30%	100.00%	Sensitivity	53.33%	34.33-71.66
		% within Disease Progression	53.30%	44.40%	50.00%	Specificity	55.56%	30.76 - 78.47
AGR before start of IT	>1.11	Count	14	10	24	Positive Likelihood Ratio	1.2	0.65 - 2.22
		% within AGR before start of IT	58.30%	41.70%	100.00%	Negative Likelihood Ratio	0.84	0.48 - 1.48
		% within Disease Progression	46.70%	55.60%	50.00%	Disease prevalence (*)	62.50%	47.35 - 76.05
	Total	Count	30	18	48	Positive Predictive Value (*)	66.67%	51.94 - 78.73
		% within AGR before start of	62.50%	37.50%	100.00%	Negative Predictive Value (*)	41.67%	28.91 - 55.64

		IT						
		% within Disease Progression	100.00 %	100.00 %	100.00%	Accuracy (*)	54.17 %	39.17 - 68.63

Table (7): Diagnostic values for Progressed events for AGR categorized at 1.11 for TMH enrolment and before start of immunotherapy.

4. Discussion

Sex and gender divergence had been observed in bladder cancer, where males had a four times higher incidence rate, and females had significantly higher rates of high-grade disease and a less than 5-year survival rate. In bladder cancer, the androgen receptor and estrogen receptor beta had been identified with gender and tumour characteristics. In RCC, the relationships were less well described. In both BC and RCC, differences in gene mutation patterns among males and females, particularly among genes located on the X-chromosome, had also been identified. Ongoing research indicates that differences in immunological, hormonal, genetic, and epigenetic factors can contribute to these divergences, but the complete mechanism that causes this divergence is currently unknown.

Age is also one of the indicators used to assess prognosis in many solid tumours, especially in clear cell renal cell carcinoma (ccRCC), and is a remarkable risk factor. In comparison to young people, older people had worse treatment results, lower survival rates, and a greater deterioration risk. This is probably related with the poor physical activity or underlying diseases in older people (24**)**. Many research studies have found differences between young and older people, but no studies have reported differences between age groups and their impact on the prognosis of patients with ccRCC (25-27).

In our study, we observed that, men had high incidence rate than women in BC and RCC. Also significantly high numbers of high-grade disease observed in BC and RCC

The role of the inflammation in cancer development has received increasing awareness in recent years. Inflammation is considered as a prominent feature and an indication of cancer. Cancer-related inflammation is correlated with the local immune reaction found at the site of the tumour, which involves tumour-derived and host-derived cytokines, small inflammatory protein mediators, and infiltrating immune cells acting in the local tumour micro-environment. Simultaneously, these inflammatory mediators also lead to systemic inflammatory responses. The release of inflammatory factors plays a major role in tumorigenesis and tumour development. Many inflammatory makers have been shown to be prognosticator of tumour prognosis.

Effective prognostic markers could be used to find out the malignant degree of the tumour, as well as to carry out risk stratification and allow individualized treatment for cancer subjects. The postoperative tumour–node–metastasis (TNM) staging system is well accepted prognostic model for RCC patients in clinical practice, but its preciseness may be unsatisfactory, with outcomes of patients at the same stage being significantly different. However, the TNM staging system can only be evaluated in patients who undergo surgery. Therefore, a new laboratory marker to

complement the current risk stratification system of RCC patients is currently required for clinical decision-making (18).

Currently many studies have indicated that there is a close correlation between pre-treatment serum albumin and tumour prognosis; especially, the low the concentration of pre-treatment serum albumin, the worst the prognosis in cancer patients 28-31.

UB is highly invasive tumour with high mortality rate. In cases where patients received radical surgery, 20%-30% of them had recurrence and distant metastasis that seriously affect the quality of life (32–34). A common predictive indicators for UB, includes tumour stage, grade and lymph node status bur it is very hard to accurately predict the prognosis of patients before treatment alone (35). Currently researchers have developed models to predict the survival outcomes in many urinary cancer patients. Zhang et al. (36) developed a model which includes the clinic-pathological features, AGR, C-reactive protein/Albumin Ratio (CAR), and Neutrophil-Lymphocyte Ratio (NLR) to predict OS and PFS after radical surgery for BC. Chen et al. used the data of T stage, AGR, NLR, and Monocyte to Lymphocyte Ratio (MLR) to construct a model and used to evaluate the survival outcome in clear cell renal cell carcinoma (ccRCC) patients (37).

Albumin and globulin are the two main proteins in the serum and correlated to nutritional status and systemic inflammation in cancer patients (38). The albumin globulin ratio (AGR) is a ratio that combines the two indexes (albumin and globulin). Current studies have disclosed that AGR is an independent prognostic factor for several cancers, for example multiple myeloma (39), non-small cell lung cancer (40), and colorectal cancer (41). However the low AGR is associated with worse survival. Furthermore, the use of AGR to evaluate the clinical prognosis in patients with UC remains controversial. Current published literature show that UC patients with low AGR have a poorer prognosis; Pradere et al. (42) identified that pre-treatment AGR is not associated with OS or recurrence-free survival (RFS).

In this present study, we examined the distribution of albumin; globulin and AGR at the time of TMC enrolment (TMH Enrol) and the pre-treatment of the ICIs therapy (before start of IT) were similar when compared with progressed and non-progressed group. The pre-treatment AGR was significantly associated with OS of the disease with p-value 0.035; hazard ratio 2.196 (95% CI – 1.057- 4.564). The PFS was not significant with p-value 0.093; hazard ratio 1.867 (95% CI – 0.901-3.869) in the pre- treatment AGR. The limitation of our study is the small cohort size.

The current studies of immune checkpoint inhibitors (ICIs) such as PD-1 inhibitors, CTLA-4 inhibitors, etc., has revolutionized the therapeutic dynamics in many solid cancers with poor clinical outcomes including genitourinary cancer. It has become a major focus of kidney cancer treatment research. In resourceful countries, most patients with advanced kidney cancer receive ICIs at some point during their treatment. A small minority of people with clear-cell kidney cancer and other rarer types of the disease have their tumours disappear entirely during treatment with these drugs.

Patients with urinary bladder cancer are also treated with immunotherapy that includes Bacillus Calmette-Guerin (BCG) vaccine as well as ICIs. BCG causes an immune system reaction that directs germ-fighting cells to the bladder and helps in cancer cell killing. More recently, ICIs have also been approved to treat bladder cancer. Pembrolizumab or Nivolumab or Atezolizumab is being used either in first line or second line therapy. These drugs help the immune system to identify and fight cancer cells.

However, these novel immunotherapy drugs are very expensive and hence less affordable in low and middle-income countries like India. Moreover, data shows that these novel immunotherapy drugs are not effective in a subset of patients. Hence, it is more relevant to use these expensive

therapies in selective patients who will benefit from such therapies. Unfortunately, no routinely available biomarker can be used to evaluate the effectiveness of these ICIs in patients with genitourinary cancers. Therefore, there is an urgent requirement to identify routinely used cost-effective, reliable, reproducible biomarkers to predict therapeutic response and clinical outcomes in patients with genitourinary cancers treated with ICIs. Furthermore, a universal prognostic factor that can predict survival regardless of the type of cancer will help to simplify the management of cancer patients.

5. Conclusion

Simple, routinely available and cost effective AGR from biochemical test has a great potential to be used as a biomarker to predict the overall survival in patients with urinary bladder cancer and RCC patients treated with ICIs.

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Competing interests statement:
The authors declare no competing interests.

ABBREVIATIONS:
A -Albumin
AGR - Albumin / globulin ratio
BC - Bladder cancer
ccRCC - clear cell Renal Cell Carcinoma
CIS - Carcinoma in situ
CI - Confidence interval
CTLA4 - Cytotoxic T- Lymphocyte – associated Antigen 4
EMR - Electronic Medical Record
G-Globulin
HPR - Histopathological Report
HR - Hazard ratio
ICIs -Immune Check Point Inhibitors
IQR -Inter Quartile Range
ISUP - International Society of Urological Pathology
IT -immunotherapy
KM - Kaplan Meier
NPV - Negative Predictive Value
OS - Overall survival
PD-1 - Programmed cell Death 1
PFS -Progression Free Survival
PPV - Positive Predictive Value
Prcc- papillary renal cell carcinoma
RCC - Renal cell carcinoma
SD - Standard deviation
TMC - Tata Memorial Centre
TNM - Tumor-Node-Metastasis
UB -Urinary bladder
WHO - World Health Organization

Author contributions:
Mrs. Shilpa Kushte collected, analysed the data and wrote the paper. Dr. Prashant Tembhare participated in the writing. Dr. Rachna Khatri, Dr. Amit Joshi, Dr. P. G. Subramanian, , Dr. Kinjalka Ghosh, Dr. Santosh Menon, Dr. Prashant Tembhare assisted in the design of this study. Mr. Akash Pawar ensured the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript.

6. References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer Statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32. doi: 10.3322/caac.21338.
2. Antoni S, Ferlay J, Soerjomataram I, et al. Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol. 2017;71:96.
3. Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. Available from: https://gco.iarc.fr/. Accessed June 6, 2021.
4. Mickisch G, Carballido J, Hellsten S, Schulze H, Mensink H; European Association of Urology. Guidelines on renal cell cancer. Eur Urol. 2001;40:252-5.
5. National Cancer Institute. Cancer Health Disparities Definitions and Examples. 2015.
6. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. doi: 10.3322/caac.21492.
7. Siegel RL, Miller KD, et al. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7.
8. Scosyrev E, Noyes K, Feng C, Messing E. Sex and racial differences in bladder cancer presentation and mortality in the US. Cancer. 2009;115:68–74. doi: 10.1002/cncr.23986.
9. Fajkovic H, Halpern JA, Cha EK, et al. Impact of gender on bladder cancer incidence, staging, and prognosis. World J Urol. 2011;29:457–63. doi: 10.1007/s00345-011-0709-9.
10. Dobruch J, Daneshmand S, Fisch M, et al. Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. Eur Urol. 2016;69:300–10. doi: 10.1016/j.eururo.2015.08.037.
11. Meehan B, Appu S, St Croix B, Rak-Poznanska K, Klotz L, Rak J, et al. Age-related properties of the tumour vasculature in renal cell carcinoma. BJU Int. 2011;107:416–24. doi: 10.1111/j.1464-410X.2010.09569.x.
12. Takada S, Namiki M, Takahara S, Matsumiya K, Kondoh N, Kokado Y, et al. Serum HGF levels in acute renal rejection after living related renal transplantation. Transplant Int. 1996;9:151–4. doi: 10.1007/BF00336393.
13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
14. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs – Part B: Prostate and Bladder Tumours. Eur Urol. 2016;70(1):106-19.
15. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management. London: NICE; 2015.
16. Babjuk M, Burger M, Comperat EM, et al. EAU guidelines on non-muscle-invasive bladder cancer (TaT1 and CIS). Eur Urol. 2022.
17. Kamat AM, Hahn NM, Efstathiou JA, et al. Bladder cancer. Lancet. 2016;388:276-81.

18. Taneja K, Williamson SR. Updates in pathologic staging and histologic grading of renal cell carcinoma. Surg Pathol Clin. 2018;11(4):797-812.
19. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6(7):655-63.
20. Delahunt B, Eble JN, Egevad L, Samaratunga H. Grading of renal cell carcinoma. Histopathology. 2019;74(1):4-17.
21. Moch H. The WHO/ISUP grading system for renal carcinoma. Pathologe. 2016;37(4):355-60. [German].
22. Mao MJ, Wei XL, Sheng H, et al. Clinical significance of preoperative albumin and globulin ratio in patients with gastric cancer undergoing treatment. Biomed Res Int. 2017;2017:3083267
23. Li J, Wang Y, Wu Y, et al. Prognostic value of pretreatment albumin to globulin ratio in lung cancer: a meta-analysis. Nutr Cancer. 2020.
24. Tang F, Lu Z, He C, Zhang H, Wu W, He Z. 53 years old is a reasonable cut-off value to define young and old patients in clear cell renal cell carcinoma: a study based on TCGA and SEER database. BMC Cancer. 2021;21(1):638. doi: 10.1186/s12885-021-08376-5.
25. Komai Y, Fujii Y, Iimura Y, Tatokoro M, Saito K, Otsuka Y, et al. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology. 2011;77(4):842–7. doi: 10.1016/j.urology.2010.09.062.
26. Kim JH, Park YH, Kim YJ, Kang SH, Byun SS, Hong SH, et al. Is there a difference in clinicopathological outcomes of renal tumor between young and old patients? A multicenter matched-pair analysis. Scand J Urol. 2016;50(5):387–91. doi: 10.1080/21681805.2016.1204621.
27. Cai M, Wei J, Zhang Z, Zhao H, Qiu Y, Fang Y, et al. Impact of age on the cancer-specific survival of patients with localized renal cell carcinoma: martingale residual and competing risks analysis. PLoS One. 2012;7(10):e48489. doi: 10.1371/journal.pone.0048489.
28. Lai CC, You JF, Yeh CY, et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. Int J Colorectal Dis. 2011;26(4):473–81.
29. Seebacher V, Hofstetter G, Polterauer S, et al. Does thyroid-stimulating hormone influence the prognosis of patients with endometrial cancer? A multicentre trial. Br J Cancer. 2013;109(1):215–18.
30. Tanriverdi O, Avci N, Oktay E, et al. Pretreatment serum albumin level is an independent prognostic factor in patients with stage IIIB non-small cell lung cancer: a study of the Turkish descriptive oncological researches group. Asian Pac J Cancer Prev. 2015;16(14):5971–6.
31. Han S, Huang Y, Li Z, Hou H, Wu A. The prognostic role of preoperative serum albumin levels in glioblastoma patients. BMC Cancer. 2015;15:108.
32. Liu J, Wang F, Li S, Huang W, Jia Y, Wei C. The prognostic significance of preoperative serum albumin in urothelial carcinoma: a systematic review and meta-analysis. Biosci Rep. 2018;38:1–13. doi: 10.1042/BSR20180214.
33. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7–33. doi: 10.3322/caac.21708.
34. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. Eur Urol. 2021;79:62–79. doi: 10.1016/j.eururo.2020.05.042.

35. Mori K, Janisch F, Mostafaei H, Lysenko I, Kimura S, Egawa S, et al. Prognostic value of preoperative blood-based biomarkers in upper tract urothelial carcinoma treated with nephroureterectomy: A systematic review and meta-analysis. Urol Oncol. 2020;38:315–33. doi: 10.1016/j.urolonc.2020.01.015.
36. Zhang W, Yang F, Kadier A, Chen Y, Yu Y, Zhang J, et al. Development of nomograms related to inflammatory biomarkers to estimate the prognosis of bladder cancer after radical cystectomy. *Ann Trans Med* (2021) 9:1440. doi: 10.21037/atm-21-4097.
37. Chen Z, Shao Y, Yao H, Zhuang Q, Wang K, Xing Z, et al. Preoperative albumin to globulin ratio predicts survival in clear cell renal cell carcinoma patients. *Oncotarget* (2017) 8:48291–302. doi: 10.18632/oncotarget.15162.
38. Chung JW, Park DJ, Chun SY, Choi SH, Lee JN, Kim BS, et al. The prognostic role of preoperative serum albumin/globulin ratio in patients with non-metastatic renal cell carcinoma undergoing partial or radical nephrectomy. *Sci Rep* (2020) 10:11999. doi: 10.1038/s41598-020-68975-3.
39. Cai Y, Zhao Y, Dai Q, Xu M, Xu X, Xia W. Prognostic value of the albumin-globulin ratio and albumin-globulin score in patients with multiple myeloma. *J Int Med Res* (2021) 49:300060521997736. doi: 10.1177/0300060521997736.
40. Guo X, Shao J, Zhai B, Zou Q, Yan J, Gu H, et al. Relationship and prognostic significance between preoperative serum albumin to globulin ratio and CT features of non-small cell lung cancer. *Eur J Radiol* (2020) 128:109039. doi: 10.1016/j.ejrad.2020.109039.
41. Quan L, Jiang X, Jia X, Cheng F. Prognostic value of the albumin-to-Globulin ratio in patients with colorectal cancer: A meta-analysis. *Nutr Cancer* (2022) 27:1–11.doi: 10.1080/01635581.2022. 2076890.
42. Pradere B, D'Andrea D, Schuettfort VM, Foerster B, Quhal F, Mori K, et al. Pre-therapy serum albumin-to-globulin ratio in patients treated with neoadjuvant chemotherapy and radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol* (2021) 39:2567–77. doi: 10.1007/s00345-020-03479-3.