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REVIEW

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Exploring racial disparities in bladder urothelial cancer: insights into survival and genetic variations

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Abstract

Background Bladder urothelial cancer is the most common malignancy of the urinary system and the 10th most common cancer worldwide with incidence appearing to show a geographical and exposure pattern. Advances in genomic technologies provide abundant data and insight into tumors at the single-cell resolution and are usually stored in repositories like The Cancer Genome Atlas (TCGA). However, data sources for the TCGA appear to be focused on European and American populations. The extent to which genomic and survival data can be applied to populations not included in the study remains somewhat uncertain.

Methods We explored the genomic and survival characteristics of the TCGA pan-cancer atlas of bladder urothelial cancer. We decluttered these characteristics based on racial groups and compared between and among the races and the overall dataset.

Results Significant variations were seen in age groups especially Asians (51–60) years and Blacks (61–70) years compared to Whites and the BLCA dataset with a statistically significant difference in mean diagnosis age ($p = 0.0048$) between Asians and the whole dataset. Overall survival characteristics were similar but genetic features were vastly different. Significant inter-racial alterations could be seen among genes involved in different pathways, oncogenes, tumor suppressors, cytoband amplification and/or deletion, mutation count, and aneuploidy scores.

Conclusion The TCGA pan-cancer atlas for bladder urothelial cancer adequately represents White populations only. The genomic features do not apply to Blacks and Asians. We recommend better coverage for other populations to ensure adequate data for clinicians and researchers.

Keywords Bladder urothelial carcinoma, TCGA, Racial disparity, Genomics, Survival

1 Background

Urothelial bladder cancer is the most common malignancy of the urinary system, the tenth most prevalent cancer worldwide, and is gradually increasing globally in industrialized nations [1]. There are about 573,000 new cases and 213,000 deaths worldwide with an approximately 4 times higher incidence in men [2, 3] with a 5-year survival rate of about 77.1%. Mortality is greatest in North and East Africa and the Middle East, where schistosomiasis infection leads to high incidence rates. Despite an increase in incidence, bladder cancer mortality has significantly decreased globally. However, death rates have risen in several nations, including the Philippines, Ecuador, and Iceland [4]. Geographically, incidence rates are highest in Europe and North America [2] with analysts predicting a steady rise in most countries except New Zealand which recorded

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a 10% decrease over a decade [1]. Incidence rates and 5-year survival among African Americans are lower than among Whites and are primarily attributable to an excess of localized tumors [5]. The lower incidence in other geographical areas like Central America and Africa was correlated to a lower human development index (HDI) [4]. The observed geographic and temporal patterns of bladder cancer incidence worldwide appear to reflect the prevalence of tobacco smoking, infection with Schistosoma Haematobium, and occupational exposures to aromatic amines and other chemicals affecting some populations [2].

Clinically, bladder cancer is classified into two distinct groups: non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). The pathogenesis of NMIBC involves genetic alterations in receptor Tyrosine kinases HRAS, FGFR3, and PIK3CA genes. A synergistic oncogenic effect is said to occur between FGFR3 and PIK3CA, while RAS and FGFR3 are mutually exclusive. Mutation in FGFR3 was found to play a crucial role in initiation of low-grade tumors by triggering the RTK/RAS/RAF cell cycle regulation pathway [6–8]. However, pathogenesis of MIBC involves alterations in tumor suppressor genes such as p16, p53, PTEN, and Rb which are associated with cell cycle control [8]. TP53 and the amplification of mdm2 (which degrades p53) is implicated in bladder cancer, and carcinogenesis of other tumors may also be associated with development of MIBC [6].

The Cancer Genome Atlas (TCGA) is a rich computational resource for the genomic and mutational data for different cancer types [9, 10] and has been helpful in genomic studies [9, 11], validation of biomarkers [12], and the design of computational oncology models [13]. This means that accuracy and robustness of the data are essential for research, modeling, and clinical usage. However, data sources in genomic sequencing appear to reveal racial disparities [14] and clinical variance. These might be due to differences in tumor biology or even environmental, biological, behavioral, and socioeconomic factors, as well as healthcare systems [15–17]. The genetic ancestry informative markers that occur within different populations to an extent contribute to cancer risk and exposure, hence relevant to cancer research [18, 19].

In this work, we explored the genomic and clinical survival characteristics of bladder cancer using the TCGA pan-cancer atlas. We investigated whether these data adequately represent all races and which race is most representative of this landmark cancer genomics database. Also, we categorized the mutations and compared the differences among each racial group for conformity to the dataset.

2 Methods

2.1 Patient data

Publicly accessible, deidentified data of patients with bladder urothelial carcinoma (TCGA Code—BLCA) were extracted from TCGA database consisting of previously compiled studies [20–26]. We reviewed tumor genetic data obtained using next-generation sequencing of 411 patients that had accompanying demographic and clinical attributes using the cBio Cancer Genomics Portal (http://cbioportal.org) [27, 28]. Patient's data were segregated by racial groups and compared to the combined BLCA dataset. Racial terms used were Asian, Black, and White as per updated guidance on the reporting of race and ethnicity in medical and science journals [29].

2.2 Tumor staging and metastasis

The American Joint Committee on Cancer (AJCC) Tumor Stage Code and AJCC-Metastasis Stage Code was the criteria used to stage patient cancer [30]. Since data were from different studies, numerical tumor stage code was used to denote numero-alphabetical codes. For example, T2 consists of both T2A and T2B.

2.3 Survival time analysis

Survival time analysis of clinical data is calculated using the Kaplan–Meier method from disease-free survival (DFS), disease-specific survival (DSS), progression-free survival (PFS), and overall survival [OS] mentioned in Patient Data section.

2.4 Genomic data

From available data, we extracted only cancer-related genes using OncoKB [31], which is based on Food and Drug Administration (FDA) labeling and National Comprehensive Cancer Network (NCCN) guidelines. We analyzed frequency of mutated genes and copy number alterations among patients. BLCA-related genes [32] and super-enhancer genes [33] are based on previous studies on bladder carcinoma.

2.5 Microsatellite instability and aneuploidy score

Microsatelitte instability was assessed using MSISensor and the more refined MSI MANTIS score [34]. The aneuploidy score reflects the total burden of autosomal chromosome arm alteration and was ranged from values of 0 through 39 [21].

2.6 Statistical analysis

Normality of data was tested using Kolmogorov–Smirnov test. Normally distributed data were analyzed

with one-way ANOVA and Dunnett's multiple comparison test; otherwise, Kruskal–Wallis and Dunn's multiple comparison tests were employed. Analyses were conducted on Prism (version 9.4.1) unless otherwise specified. Mantel-Cox (log-rank) test was used to compare difference between survival curves. A p value less than 0.05 was considered to be statistically significant.

3 Results

3.1 Significant demographic deviation in racial groups

Available data were skewed toward White populations with 79.6% of total patients while Asians and Blacks accounts for the remaining data. Only Asians have patients younger than 40 years old (4.65%) with Blacks and Whites having no representative. Of note also is that the most commonly diagnosed age group is 51–60 in Asians, 61–70 in Blacks and 71–80 in Whites indicate that the overall BLCA dataset (71–80) is skewed toward White population (Fig. 1A). There was a statistically significant difference ($p=0.0048$) between mean diagnosis age between Asians and the BLCA dataset (Fig. 1B) revealing that Asians are not adequately captured in diagnosis age. Males are more commonly affected with bladder urothelial cancer than females (Fig. 1C), but the male:female ratio for Blacks (1.3:1) was lower than other groups (2.8:1 to 4.4:1).

3.2 Tumor and survival characteristics

The BLCA dataset suggests that most patients are diagnosed with a T3 tumor stage (Fig. 2A). However, racial detachment indicates that most Asians and to a lesser degree Blacks present with T2 stage. Only Asians were found to have patients with T1 stage, and most patients with a T4 presentation were Blacks. As for metastasis, the BLCA dataset postulates an even distribution between M0 and MX. Analysis based on race groups shows that Asians have a significantly larger proportion of patients at M0, minimal MX presentation, and virtually no patient presenting with an M1 status. Overall, findings suggest that Asians presented with less advanced disease. We also analyzed for differences in patient survival (Fig. 2B) and found no statistically significant aberration in disease-free ($p=0.4391$), disease-specific ($p=0.3020$), progression-free ($p=0.3048$), and overall survival ($p=0.4338$) among all race groups and BLCA dataset. Perhaps, an indication of similar success in patient management among all groups.

3.3 Wide variation in gene mutations among racial groups

In the BLCA dataset, about 50% of patients had a mutation in the TP53 gene. The same pattern is seen in Blacks (47.8%) and Whites (53.1%) with about half of patients having this mutation. In Asians however, FGFG3 and KDM6A (27.9%) were the most common mutation with TP53 mutation occurring in about 20%

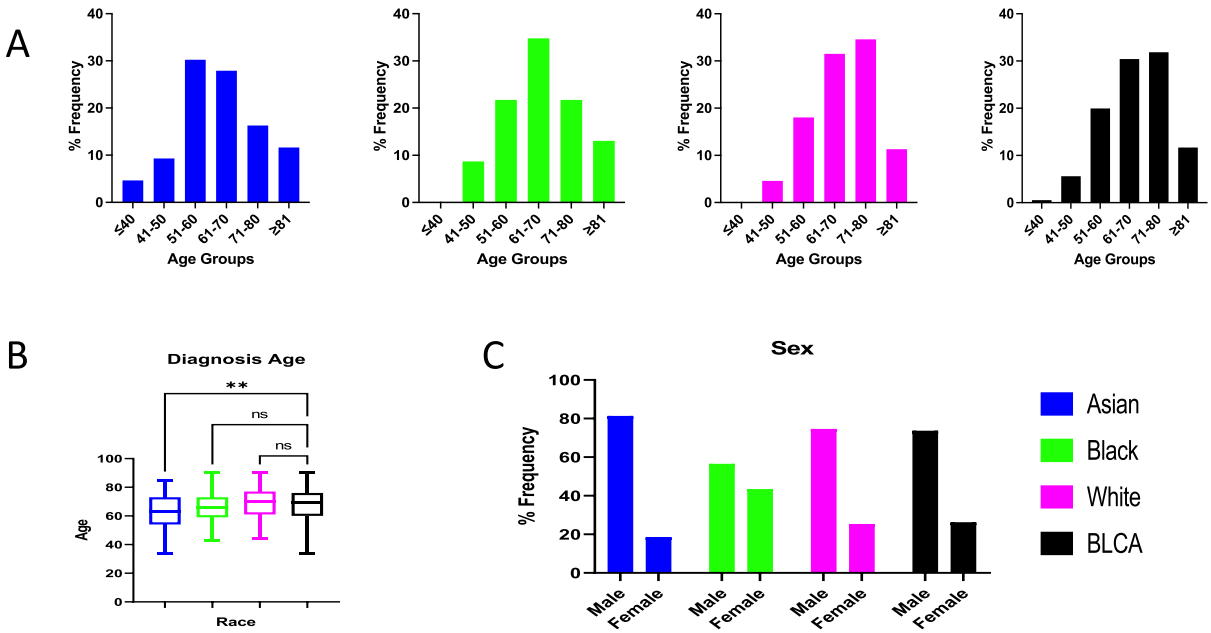

Fig. 1 Demographic deviation of racial groups from BLCA dataset. Stratification of patients by age groups (**A**), mean diagnosis age (**B**), and sex (**C**) of patients in the BLCA dataset. Data were compared between different racial groups and the BLCA dataset for conformity

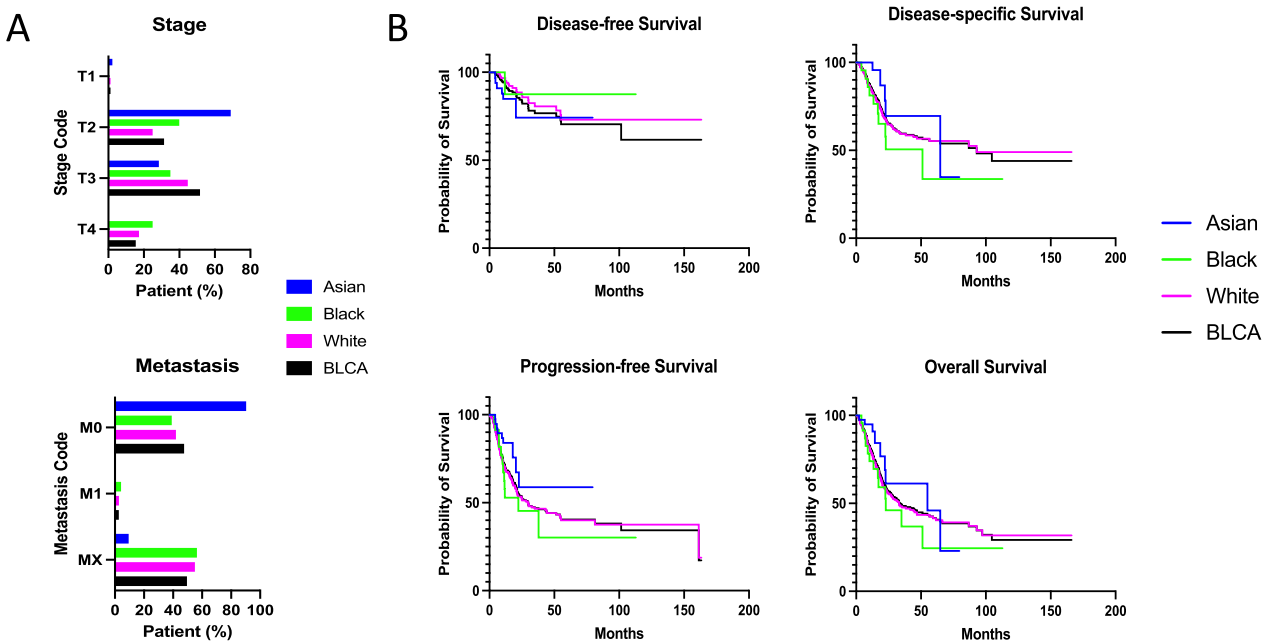

Fig. 2 Tumor and survival characteristics. Racial groups were analyzed for differences in their cancer stage (**A**) and metastasis status. Survival curves based on the Kaplan–Meier method were assessed for disease-free survival, disease-specific survival, progression-free survival, and overall survival for patients from all racial groups and BLCA dataset. Note—T2 comprises T2A and T2B, T3 comprises T3A and T3B, and T4 comprises T4A and T4B. we fococuses more on the relevant data among Asians with a significant number of patient M0, Mx and no patiets with M1 status as shown in fig. 2 (**B**)

of patients. A previous study [32] reviewed bladder urothelial cancer-related genes but in terms of racial conformity, only ERBB2, ELF3, and KDM6A shows similar findings among racial groups. The vast majority of mutated genes were similar between Whites and the BLCA dataset with genes like ARID1A and ERBB3; in some cases, there is no mutation in some genes like NFE2L2 and KLF5 in Asians or ERBB3 in Blacks. Well-known oncogenes like MYC and WWTR1 mutations are higher in Blacks and totally undetectable in Asians while tumor suppressors like TP53 and RB1 were also low in Asians. Asians had the highest alteration frequency in super-enhancer genes—PPARG and FGFR3 [33] as well as the Wnt signaling genes—CTNNB1 and LRP6. Patients with mismatch repair deficiency usually show remarkable response to PD-1 blockade [35]. Here, we observe that Blacks only have mutation in MLH1, and Asians only have mutation in MSH2; Whites on the other hand (as seen in BLCA dataset) have mutations in all the five identified mismatch repair genes. In addition, Blacks had higher mutations in checkpoint genes, Fanconi Anemia-related genes, and BRCA1 compared to other groups. Overall, genetic alteration frequency in BLCA dataset is more representative of White population than other racial groups (Fig. 3).

3.4 Copy number alteration pattern among racial groups

Cytobands with chromosomal abnormality show great variance in terms of genomic amplification (Fig. 4A). Of note is the dominance of 1q23.3 amplification in Asians, 11q13.3 amplification in Blacks, 6p23.3 amplification in Whites, and surprisingly 1q23.3 amplification in BLCA dataset. Even with marked difference in genetic mutation between Asians and the BLCA dataset, the most common amplified cytoband is strikingly the same. Cytobands with homologous deletion are very similar with a dominance of 9p21.3 deletion (genes—CDKN2A, CDKN2B and MTAP) in all racial groups. We only observed a relatively high alteration (4.7% of patients) in the X chromosome—Xq13.1 and Xq12 only in Asians. Tumor mutational burden (Fig. 4B) of Asians was significantly different with BLCA dataset ($p = < 0.0001$) and among groups ($p < 0.0001$). Similarly, aneuploidy score (Fig. 4C) of Asians was also significantly different with BLCA group ($p = 0.0010$) and among groups ($p = 0.0017$). Bladder urothelial cancer is usually microsatellite stable [36]. The same pattern was seen (Fig. 4D) in all racial groups and BLCA dataset with no statistical deviation.

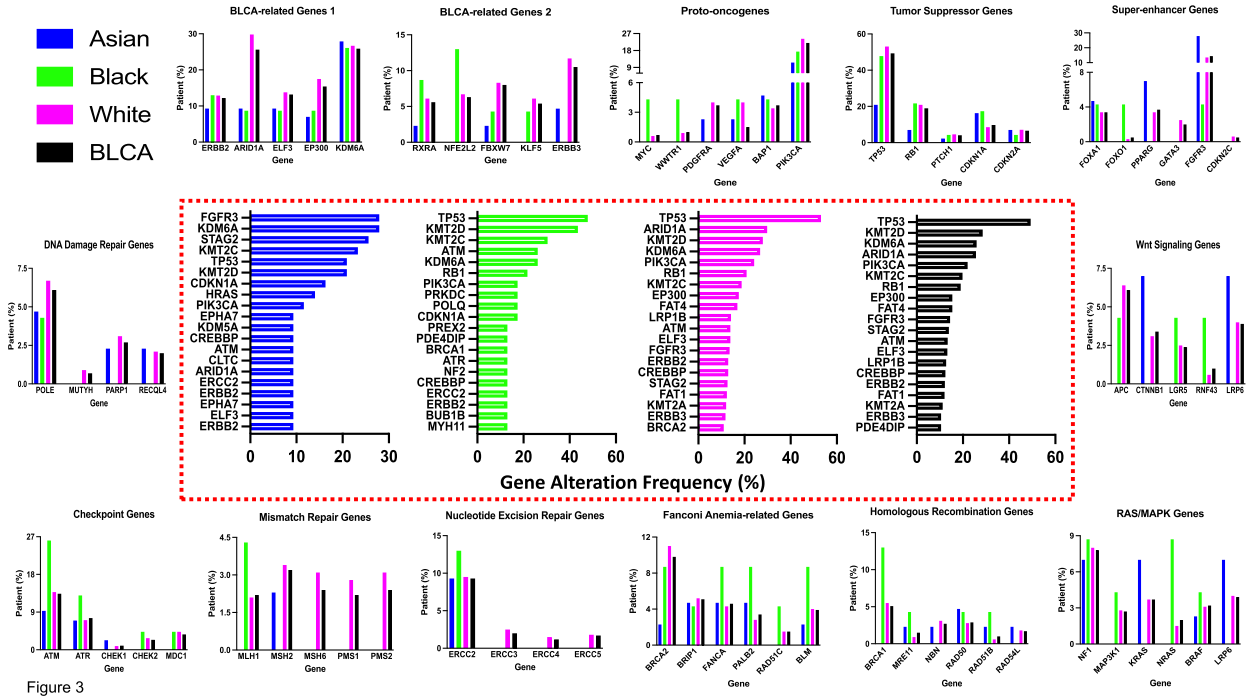

Figure 3

Fig. 3 Genetic variation among racial groups. Genetic analysis from tumor samples of different racial groups shows varying differences in mutated genes. Only cancer-related genes were analyzed and were grouped based on function, pathway, or other publications. Central panels in red-dotted lines indicate the top 20 most commonly mutated genes and their gene alteration frequency among racial groups

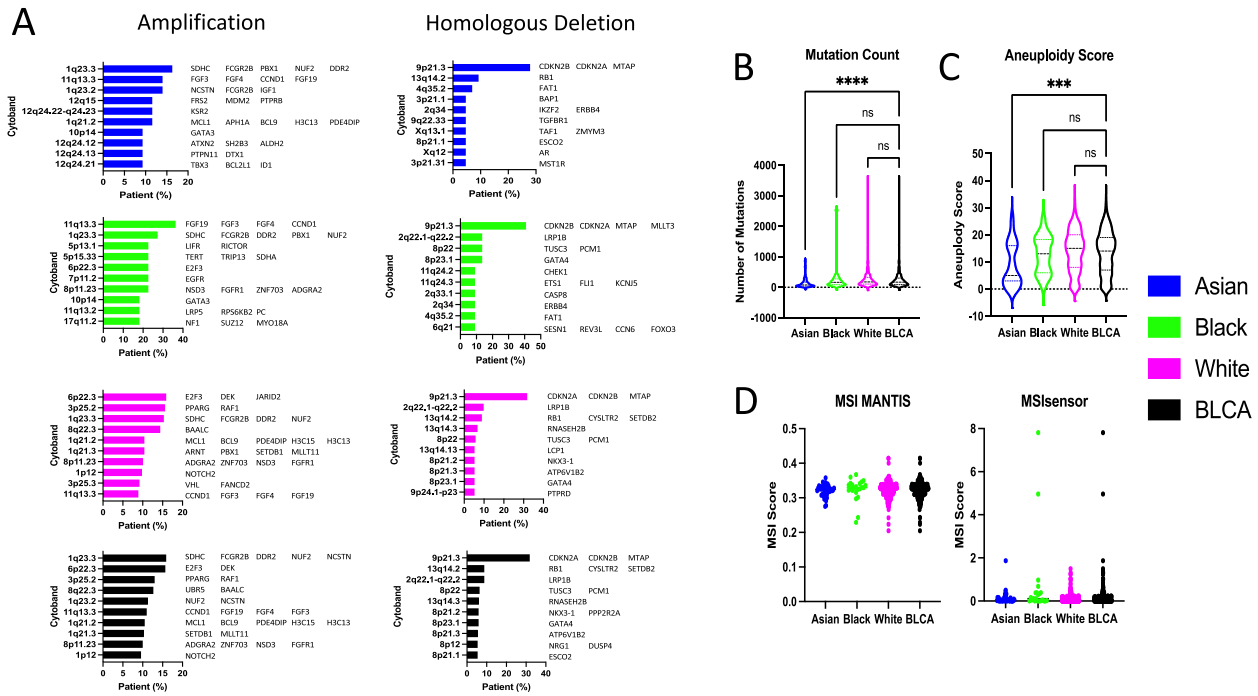

Fig. 4 Copy number alteration pattern among racial groups. Commonly altered cytobands with gene amplification and homologous deletion shown for all racial groups and BLCA dataset (**A**). Genes located in the cytobands are shown to the right of each horizontal bar. Violin plot shows total mutation count per patient (**B**) and aneuploidy score (**C**) in all racial groups and BLCA dataset. Dot plots (**D**) show microsatellite instability score using MSI MANTIS and MSISensor for all racial groups and BLCA dataset

4 Discussion

Bladder cancer is one of the top ten common tumors of the body [37]. In this study, we observed that the White populations were the most represented in this dataset comprising a total of 79.6% of the patients while Asians and Blacks have the lowest representation. The findings echo available data [1] which suggest a high incidence of bladder cancer in Europe and North America, but we suspect this to be as a result of sampling bias. The observed differences in the age groups where 4.65% of Asians were less than 40 years old seem to be at variance with studies, showing that Whites are more frequently diagnosed at a younger age [37]. The commonly diagnosed age group declines from 71–80 in Whites, 61–70 in Blacks, and 51–60 in Asians showing which is in stark contrast to documented findings that suggest all races are diagnosed at about age of 70–79 [38]. We found that males have the highest frequency of the urothelial bladder cancer which is in line with the findings in other studies [1, 3, 37, 38], possibly due to differences in exposure to risk factors [1, 37]. Our findings also pose a question—is the low male:female ratio in Blacks due to exposure to risk factors or other socioeconomic factors?

The present study indicates that most Asians presented with an earlier tumor stage of T2 compared to other races. As for late presentation—T4 stage, most of the patients were Blacks, while the BLCA datasets suggest that most patients were diagnosed with a T3 tumor stage. Only Asians were found to have patients with a T1 stage. The overall findings with respect to cancer staging indicate that majority of the patients across all racial groups and BLCA dataset were diagnosed with a T2 stage. This study presented some similarity as well as disparity to a study by Shu and colleagues who reported a higher presentation of T1, T3, and T4 stages in Blacks and to a lesser degree Asians, while Whites were found to have the highest presentation of T2 stage followed by Asians [19]. This indicates that multiple potential factors such as availability and access to cancer therapy, appropriate cancer surveillance, lymph node dissection, and radical cystectomy might contribute to disparities in bladder cancer stage presentation among different ethnic/racial groups.

The BLCA dataset suggests an even distribution between M0 and MX with regards to metastasis, with minimal presentation in M1. Analysis of metastasis based on race shows that Asians have a significantly larger proportion of patients at M0, minimal MX presentation, and virtually no patient presenting with an M1 status. Overall, findings suggest that Asians presented with less advanced disease, while Blacks presented with more advanced disease. These findings suggest that racial disparity exists between ethnic and racial groups with respect to bladder cancer disease progression, which might be due to increased miR-34b and miR-886-5p expression in Blacks as compared to other ethnic groups. A study conducted on Iranian bladder cancer patients reported that patients with advanced metastasis presented with overexpression of microRNAs miR-34b, miR-886-5p, miR200c, miR-30b, miR-141, and miR-21-5p [39]. These microRNAs induce tumor cell proliferation, migration through PTEN regulation, and negative regulation of apoptosis [40].

Patient survival was analyzed in this study, and no statistically significant aberration was found in disease-free, disease-specific, progression-free, and overall survival in the BLCA dataset and all race groups. However, other studies reported that Blacks have the least chances of surviving. A study reported that among patients diagnosed with bladder cancer in Ohio cancer registry, Black women had a 68% risk of dying than White men [41]. Another finding reported a sharp increase in cancer-specific mortality after 24-month follow-up despite differences in bladder cancer severity at the time of presentation and found worst survival rate among female and African American patients [19]. This disparity might be attributed to differences in disease stage at diagnosis, utilization of cancer therapy, biologic factors, social determinants of health, diet, physical activity, and socioeconomic factors as females and African American bladder cancer patients are known to present with more advanced stage of cancer and are more at risk of occupational exposure associated with bladder cancer than Whites and Asians [19, 37, 41–46].

Earlier findings [47] which identified the prevalence of clonal mutations in several significantly mutated genes (SMGs) show variation among different race groups with Black and White patients showing higher fractions of clonal TP53 mutations than Asian patients. The frequency of FGFR3, NRAS, TSC1, and ELF3 mutations was higher in Blacks than Whites and showed higher frequencies of clonal mutations in Whites than in Asian patients. It is interesting to note that, FGFR3 clonal mutations were observed to occur more frequently not only in Asian patients, but FGFR3 mutations are the early driver events during non-muscle invasive bladder cancer (NMIBC) evolution, and we also observed that FGFR3 clonal mutations occurred more frequently in NMIBC than in muscle invasive bladder cancer (MIBC) [47]. Activating mutations in FGFR3 are the most common and most specific genetic variation in noninvasive bladder cancer. The T allele accounts for 70% of non-muscle-invasive bladder cancer and is associated with an increased expression of FGFR3 in adipose tissue, which was used

as a surrogate tissue due to lack of expression data from normal urothelial tissue [48]. The result obtained from the previous study revealed that the most frequently mutated genes were tumor suppressor genes TP53, APC, FAT1, RB1, BRCA2, and NF1 with TP53 and showed a high frequency of mutation across all cancer types [49]. Numerous studies have shown that mutations of TP53 are associated with poor prognosis in cancer [49]. Therefore, genomic stability regulated by TP53 may be a reason attributed to cancer disparities among different racial groups. From our findings, we also observed that Blacks may potentially not respond well to PD1 blockade due to having an intact mismatch repair gene [35].

Our analysis found a higher amplification of 12q cytoband specifically in Asians compared to the other racial groups and BLCA dataset. A study by Basu and colleagues [50] reported a complete amplification of 12q and frequent losses at 3p24.2–24.1 (20%), 5q11.1–35.3 (40%), 6q25.3–27 (40%), 9p24.3–21.5 (60%), and 9q21.11–33.3 (40%) in patients exposed to high Arsenic content. They also found that 2p25.3, 4p16.3, 7p22.3, 10q26.13, 16q24.3, 17p11.2, 19q13.33, and 20q13.33 cytoband regions showed ≥ 40% amplification while in the present comparative study, none of the above regions showed up to 20% amplification in BLCA, with only 11q13.3 appearing in Blacks. We also showed that 9p21.3 (genes—CDKN2A, CDKN2B, and MTAP) cytoband to be the most frequently deleted region with Blacks accounting for 43%, Whites and BLCA dataset accounting for 34% each, and Asians accounting for 28%. These findings are at variance with the study by Basu and colleagues [50] further suggesting a pan-cancer atlas study involving various cohorts might yield entirely different findings due to heterogeneity of the population. Blacks had the highest amplification (38%) of the 11q13.3 cytoband (genes—FGF4, FGF3, FGF19, and CCND1) which is prevalent in many other tumors [51] and the highest frequency of deletion (43%) of the 9p21.3 cytoband (genes—CDKN2A, CDKN2B, MTAP, and MLLT3) which favors immune evasion and metastasis [52]. We found that Whites and BLCA dataset accounted for the highest Tumor Mutational Burden, followed by Blacks, while Asians accounted for the least TMB in our comparison. A higher tumor mutational burden has been correlated with longer survival after immune checkpoint inhibitors and a poorer survival without immunotherapy [53]. Similarly, aneuploidy score differed significantly in Asians compared to the other groups indicating a potentially poorer prognosis in such populations [54]. All groups revealed a microsatellite stable tumor as confirmed by numerous [36].

5 Conclusion

In summary, we found an overrepresentation of Whites in the TCGA dataset which is a reference database and reliable repository for cancer genomics. The overall genomic and clinical data are by and large representative of the White population. The survival data could be applicable for Asians and Blacks, but the genomic information is quite different. We recommend the acceleration of data uptake from diverse geographical areas to augment the available data in the database. It is still not completely clear if the racial differences seen are due to limited sample size in racial groups or a true representation of such populations. Poor funding and limited collaborations might be implicated in these circumstances but nevertheless, more data are needed from Africa and Asia to overcome this possible sampling bias.

Abbreviations

TCGA	The Cancer Genome Atlas
HDI	Human development index
NMIBC	Non-muscle invasive bladder cancer
MIBC	Muscle invasive bladder cancer
BLCA	Bladder cancer
T	Tumor stage
DFS	Disease-free survival
DSS	Disease-specific survival
PFS	Progression-free survival
OS	Overall survival
FDA	Food and drug administration
MSI	Microsatelitte instability
ANOVA	Analysis of variance
M	Metastasis
SMGs	Significantly mutated genes

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Author contributions

SDA, ZMB, SSG, and IMK conceptualized and jointly wrote the manuscript. SDA did the analyses.

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Availability of data and materials

The dataset analyzed during the current study is available in the cBio Portal for Cancer Genomics at https://www.cbioportal.org/study/clinicalData?id=blca_tcga_pan_can_atlas_2018

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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