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Observed racial disparity in the negative predictive value of multi-parametric MRI for the diagnosis for prostate cancer

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Abstract

Objective To evaluate the trend that despite recent advances in the screening, diagnosis, and management of prostate cancer (PCa), African-Americans (AAs) continue to have poorer outcomes compared to their Caucasian (CAU) counterparts. The reason for this may be rooted in biological differences in the cancer between the two groups; however, there may be some inherent disparities within the efficacy of the screening modalities. In this study, we aim to evaluate the negative predictive value (NPV) of multi-parametric MRI (mpMRI) between AA compared to CAUs.

Methods All mpMRI between January 2014 and June 2017 were evaluated. The MRIs were read by dedicated genitourinary radiologists. Subsequently, the readings were correlated to final pathology after the patients underwent radical prostatectomy. The NPV and negative likelihood ratios (−LR) of mpMRI were evaluated in AAs versus CAUs based on four cutoffs (≥ Grade I, ≥ Grade II, ≥ Grade III and ≥ Grade IV).

Results The mpMRI was almost equally as effective between AAs and CAUs in excluding Grade III (NPV = 89 and 94, respectively), and Grade IV or above (NPV = 96 and 98, respectively) PCa; however, the NPV of mpMRI was significantly lower for Grade I (NPV = 32 and 52, respectively) and Grade II (NPV = 50 and 79, respectively) PCa.

Conclusion Despite advances in the screening for PCa, there are disparities noted in the efficacy of screening tools between AAs and CAUs. For this reason, patients should be risk stratified and their screening results should be evaluated with consideration given to their baseline risk.

Keywords Prostate cancer · Multi-parametric MRI · Racial disparity · Negative predictive value

Abbreviations

AA	African-American
CAU	Caucasian
mpMRI	Multi-parametric magnetic resonance imaging
NPV	Negative predictive value
PCa	Prostate cancer
PI-RADS	Prostate Imaging Reporting and Data System
PSA	Prostate-specific antigen
csPCa	Clinically significant prostate cancer
EAU	European Association of Urology
PSAD	PSA density

Introduction

Prostate cancer (PCa) remains the most common male visceral cancer in the USA, with an estimated annual diagnosis and mortality of 220,800 and 27,540 men, respectively [1]. With the evolving landscape in disease diagnosis and

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management, there is an increased emphasis on identifying interventions that reliably aid in early diagnosis and cure [2]. Multi-parametric magnetic resonance imaging (mpMRI) has emerged as a diagnostic tool with high sensitivity and specificity that leads to significant increase in detection of clinically significant prostate cancer (csPCa) [3]. While the utility of obtaining pre-biopsy mpMRI in patients with no previous biopsies is not well supported, there is increasing evidence that obtaining an MRI prior to repeat biopsy may assist with targeting suspicious lesions [3–5]. Some authors have supported even utilizing mpMRI to triage patients to obviate the need for unnecessary prostate biopsies [6]. A recent meta-analysis by Moldovan et al. evaluated this exact idea by assessing the negative predictive value (NPV) of mpMRI. They found the median NPV of mpMRI to be 82.4% for overall cancer and 88.1% for csPCa [7]. However, the NPV decreased to 67% when the PCa prevalence increased from 30 to 60%. Based on these findings, the European Association of Urology (EAU) guidelines recommend patient risk stratification prior to pre-biopsy mpMRI [7].

One example of a high-risk population that may benefit from pre-biopsy risk stratification is African-Americans (AAs). Despite advances in the diagnosis and management of PCa, AA men continue to have disproportionately worse outcomes than their Caucasian (CAU) counterparts [8]. The incidence of prostate cancer is 60% higher in AAs, with a two- to threefold increased risk of mortality [9]. The reason for these variabilities in outcomes may be multifactorial with inherent differences in cancer biology, socioeconomic factors, and apprehension of the health-care system [10–12] In regards to patterns in mpMRI use, race, age, and type of insurance have an observable effect on the frequency of staging MRI for non-metastatic PCa patients undergoing radiation therapy [13]. Furthermore, AAs tend to harbor more clinically aggressive disease at the time of diagnosis, which further demonstrates the need for personalized medicine for this group [14]. All these reasons have led to increased support for implementing separate screening guidelines for high-risk groups such as AA men [8].

In this study, we aim to evaluate the effect of race on the NPV of mpMRI to further elucidate factors that may impact poorer prognosis in AA male compared to CAUs. We hypothesize that inherent characteristics of the disease in AA combined with various factors related to the prostate (size, zonal anatomy) may contribute to decreased efficacy of mpMRI in detecting csPCa.

Methods

After institutional review board approval, a retrospective review of AA and CAU patients with valid mpMRI at our institution between January 2014 and June 2017 was performed. Patients were included in the study if they had a pair of mpMRI of the prostate and TRUS biopsy within 12 months of each other. Patients with non-diagnostic mpMRI were excluded (e.g., hip implants or artifacts, extensive post-biopsy changes/hemorrhage, or previous hormonal or radiation therapy).

All mpMRIs were read according to the standardized PI-RADS (Prostate Imaging Reporting and Data System) as recommended by the European Society of Urogenital Radiology (ESUR)—version 1 until April 2015, and version 2 thereafter. All reads were performed by one of the four dedicated genitourinary radiologists with an average experience of 15 years. All radical prostatectomies were performed by one of the three high volume surgeons at our institution.

Variables that were assessed included age, race (AA versus CAU), PSA, PSA density (PSAD), BMI, abnormal digital rectal exam status, Index lesion PI-RADS score, MRI prostate volume, and TRUS biopsy Gleason score. The NPV and negative likelihood ratios (−LR) of mpMRI were evaluated in AAs versus CAU based on four cutoffs ($\geq 3+3$ [Grade I], $\geq 3+4$ [Grade II], $\geq 4+3$ [Grade III], and $\geq 4+4$ [Grade IV]).

Fagan nomograms were utilized to visualize the effect of the −LR on the probability of prostate cancer disease. Due to the well-known difference of prevalence, pre-test probabilities were calculated separately in AAs and CAUs based on the aforementioned cutoffs (number of diseased/number total cohort). Pre-test probability is the probability of the screened person having the disease in a certain population, i.e., the prevalence of disease. Post-test probabilities were obtained from Fagan nomograms after applying the negative likelihood ratios of mpMRI in AAs and CAU.

Categorical variables were provided as counts and percentages, while continuous variables were shown as medians and interquartile ranges (IQR). Variables were evaluated in the race groups utilizing the Mann–Whitney *U* and Chi-squared tests for continuous variables and categorical variables, respectively (Table 1). Study statistical analyses were two tailed and performed using R package software, version 3.5.1 [15]. A p value < 0.05 was considered statistically significant.

Results

A total of 638 patients constituted the study population. Of these, 499 patients (78%) were CAUs and 139 patients (22%) were AAs. AAs demonstrated a higher median PSA (7.00 vs 5.96, $p = 0.003$) and median PSAD (0.17 vs 0.14, $p = 0.02$). Also, AAs had higher incidence of Gleason score 7 (51% vs 34%), and GS ≥ 8 (14% vs 11%, $p < 0.001$). (Table 1).

AAs consistently demonstrated lower NPVs and −LRs for PCa on mpMRI than their CAU counterparts. In a subgroup

Table 1 Descriptive statistics of the cohort

	Total ($n=638$)	African-Americans ($n=139$)	Caucasians ($n=499$)	p
Age: median (IQR)	65 (60, 70)	64 (59, 69)	66 (60, 70)	0.067*
BMI: median (IQR)	28.8 (25.8, 32.3)	29.6 (26.3, 33)	28.6 (25.8, 32)	0.145*
Abnormal DRE (%)	61 (9.6)	12 (8.6)	49 (9.8)	0.797[a]
PSA: median (IQR)	6.3 (4.6, 9.4)	7.0 (5.2, 9.8)	5.97 (4.6, 9)	***0.003****
PSAD: median (IQR)	0.15 (0.09, 0.25)	0.17 (0.10, 0.28)	0.14 (0.09, 0.23)	***0.016****
MRI prostate volume: median (IQR)	42.5 (30, 61.6)	39.2 (28.1, 62)	42.6 (30.4, 61.3)	0.508*
MRI prostate final PI-RADS (%)				0.582[a]
1	98 (15.4)	19 (13.7)	79 (15.8)	
2	56 (8.8)	9 (6.5)	47 (9.4)	
3	137 (21.5)	34 (24.5)	103 (20.6)	
4	184 (28.8)	44 (31.7)	140 (28.1)	
5	163 (25.5)	33 (23.7)	130 (26.1)	
Gleason score at biopsy (%)				***< 0.001***[a]
Negative	318 (49.8)	27 (19.4)	163 (32.7)	
6	130 (20.4)	21 (15.1)	109 (21.8)	
7	241 (37.8)	71 (51.1)	170 (34.1)	
≥ 8	77 (12.1)	20 (14.4)	57 (11.4)	
GS ≥ 3 + 4 (%)	318 (49.8)	91 (65.5)	227 (45.5)	***< 0.001***[a]
GS ≥ 4 + 3 (%)	151 (23.7)	45 (32.4)	106 (21.2)	***0.009***[a]

Bolditalics signify statistically significant variables

*Mann–whitney *U*

[a]Chi-square

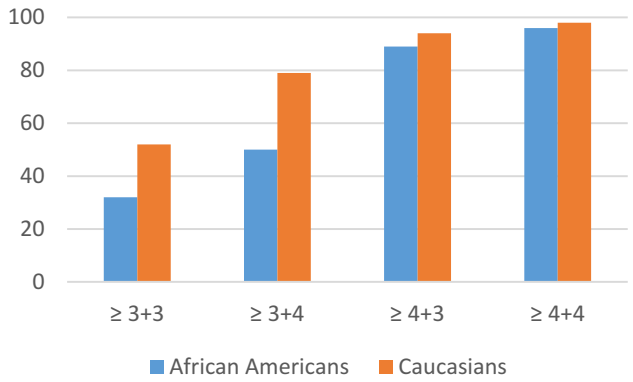

Fig. 1 Negative predictive values of different cutoffs in African-Americans versus Caucasians

analysis with cutoffs of ≥ 3 + 3 (Grade I), ≥ 3 + 4 (Grade II), ≥ 4 + 3 (Grade III), and ≥ 4 + 4 (Grade IV), AAs had an NPV of 32%, 55%, 89, and 96% compared to 52%, 79%, 94%, and 98% for CAUs (Fig. 1). In terms of −LRs, AAs showed ratios of 0.5, 0.4, 0.3, and 0.2 for the subgroups listed above, compared to 0.4, 0.3, 0.2, and 0.1 in CAUs, respectively (Table 2).

According to Fagan nomograms, mpMRI was better able to exclude low-grade disease in CAUs compared to AAs utilizing cutoffs ≥ Grade I and ≥ Grade II. At a cutoff of ≥ Grade I, CAUs had a pre-test probability of 67.3% and showed a post-test probability of 43%, while AAs had a pre-test probability of 80.6% and showed a post-test probability of 67% (Fig. 2). At a cutoff of ≥ Grade II, CAUs had a pre-test probability of 45.5% and showed a post-test probability of 18%, while AAs had a pre-test probability of 65.5% and showed a post-test probability of 50%. At higher-grade cancers, mpMRI's ability to exclude disease

Table 2 Negative predictive values, negative likelihood ratios, and pre-test and post-test probabilities evaluated by race

	African-Americans				Caucasians			
	Pre-test p	NPV	−LR	Post-test p	Pre-test p	NPV	−LR	Post-test p
≥ 3 + 3 (Grade I)	80.6	32	0.52	67	67.3	52	0.43	43
≥ 3 + 4 (Grade II)	65.5	50	0.5	50	45.5	79	0.3	18
≥ 4 + 3 (Grade III)	32.4	89	0.3	11	21.2	94	0.2	6
≥ 4 + 4 (Grade IV)	14.4	96	0.2	3	11.4	98	0.1	1.5

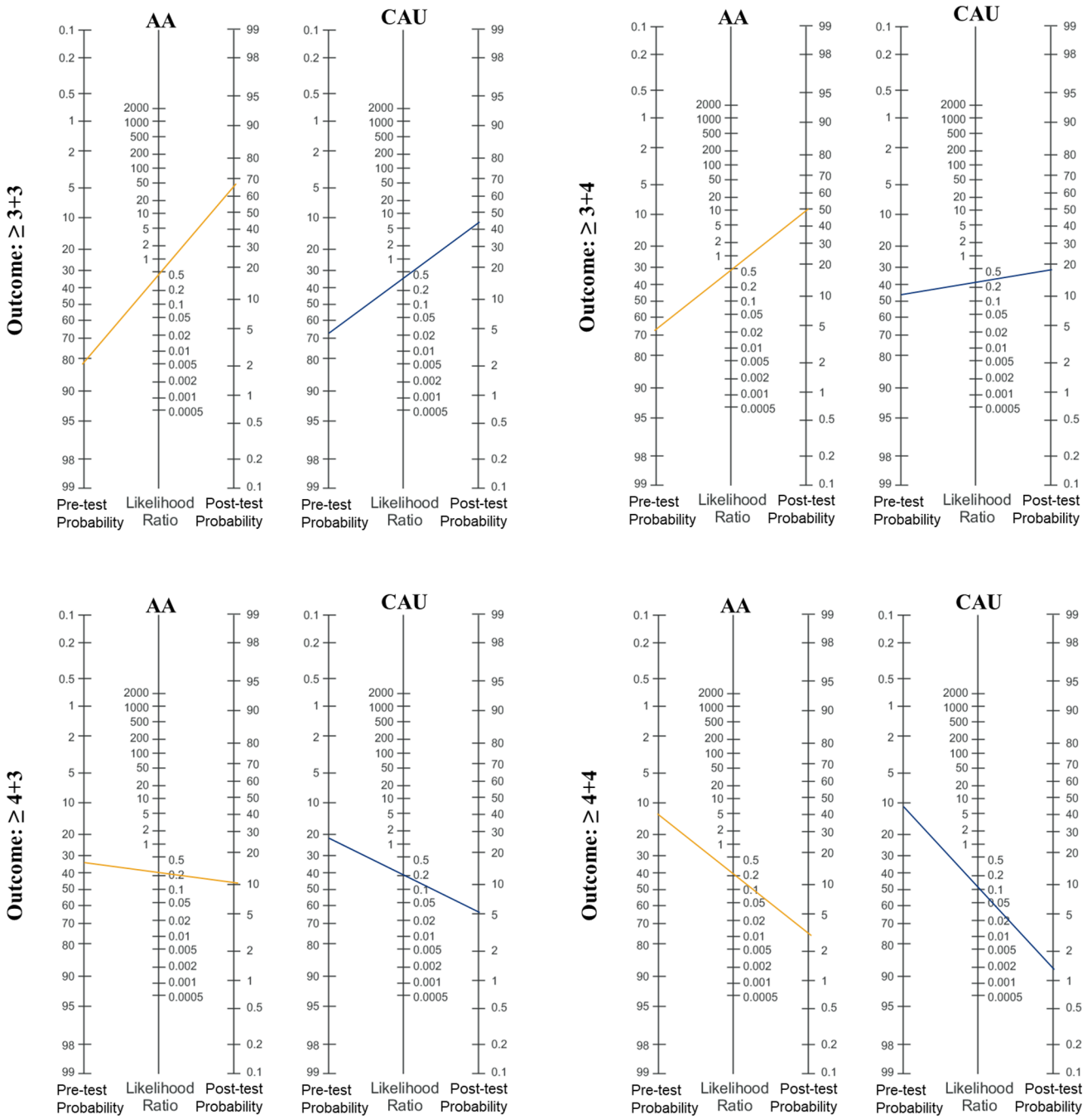

Fig. 2 Fagan nomograms based on the negative likelihood ratios from the different groups

was consistently superior in CAU compared to AAs; however, the differences are small. At ≥ Grade III, CAUs had a pre-test probability of 21.2% and showed a post-test probability of 6%, while AAs had a pre-test probability of 32.4% and showed a post-test probability of 11%. At ≥ Grade IV, CAUs had a pre-test probability of 11.4% and showed a post-test probability of 1.5%, while AAs had a pre-test probability of 14.4% and showed a post-test probability of 3%. (Table 2, Fig. 2).

Discussion

Significant variability in PCa-specific outcomes and mortality has been reported in AAs compared to their CAU counterparts [16]. AAs have a 60% higher incidence of PCa and a significantly higher mortality [8, 9, 14]. While these findings are most likely multifactorial, it is important to explore modifiable factors that may ameliorate these drastic differences in outcomes. One such factor may be improving

surveillance, as there may be inherent differences in the PCa that is seen in AAs compared to CAUs. There have been efforts made to advocate for separate screening guidelines for patients of AA descent [10]. While no definitive etiology has been identified thus far to be the sole cause of the disparity, noticeable disparity has been seen in the zonal anatomy, PSAD, and prostate size [2, 11]. Moreover, race has an observable effect on the staging prostate MRI for non-metastatic PCa patients undergoing radiation therapy [13]. With the increasing use of mpMRI prior to prostate biopsy, we aimed to evaluate whether there is a difference in the NPV of mpMRI between AAs and CAUs. If we can identify variations in the utility of this promising screening tool, then we can counsel our patients accordingly to optimize outcomes.

In this study, we found the NPV of mpMRI between CAUs and AAs to be similar when evaluating ≥ Grade III and ≥ Grade IV diseases (Table 2). However, the NPV is significantly lower in AAs undergoing mpMRI, compared to CAUs for ≥ Grade I and ≥ Grade II diseases (Table 2). Stated differently, mpMRI is equally as effective in excluding Grade 3 or Grade 4 disease, but it is significantly worse at excluding Grade 1 or Grade 2 diseases. These findings are important because this cohort of men with Grade I and Grade II PCa are the most likely to benefit from active surveillance. Therefore, if we cannot accurately exclude the presence of disease, then how can we confidently counsel them to avoid definitive therapy?

The clinical significance of this is seen in a dramatic finding recently published by Mahal et al., where they found the greatest variance in survival based on race was seen in low-grade Gleason 6 disease [17]. In fact, they found black men were twice as likely to die from Grade I disease compared to non-black men, a finding that becomes more disparate with a longer follow-up [17]. Interestingly, these findings were noted even after accounting for socioeconomic status. Based on published literature, the utilization of reliable screening and staging tools such as mpMRI may address these disparities; however, based on the findings from our cohort, it is controversial if we can confidently exclude the presence of lower-grade PCa in AA men [18]. Furthermore, AAs are significantly more likely to undergo disease upgrading (27.3% v 14.4%; $p < 0.001$), positive surgical margins (9.8% v 5.9%; $p = 0.02$), and higher Cancer of the Prostate Risk Assessment Post-Surgical scoring system (CAPRA-S) scores [16]. All of these listed findings further complicate the decision to place AA males on active surveillance or watchful waiting, as we may be grossly understaging or undertreating csPCa in AAs.

As mentioned previously, the underlying etiology of the noted disparity is most certainly multifactorial. Perhaps, the cancer biology in AAs is inherently different than that seen in CAUs, or there may be differences in the patterns of care or prognostic values of biopsy in AAs. What we can say is that even with the evolving landscape in PCa screening and management, AAs are not experiencing the same benefits from the interventions as CAUs.

There are several limitations to our study. First is the retrospective nature of the study, which may predispose the study to unadjusted confounding variables. Secondly, there is a significantly higher number of CAUs compared to AAs in the study (499 versus 139, respectively). Overall, the cohort with high-grade disease comprised a relatively small cohort in both groups. Lastly, there were different versions of PI-RADS system utilized over the time period of this study; however, there is robust evidence in support of the excellent concordance between the two versions [19, 20].

Conclusion

Racial disparity with regard to PCa is well established. This study demonstrates that the NPV of mpMRI is significantly lower in AAs than their CAU counterparts. This finding comes at a time when the role of mpMRI in the management of PCa is evolving, and more clinicians are incorporating this into their management algorithm. Ultimately, patients should be risk stratified based, and the findings of the mpMRI should be evaluated with consideration given to their clinical presentation and pre-test probability/likelihood of disease.

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Compliance with ethical standards

Conflict of interest Amr Mahran, MD, declares that he has no conflict of interest. Kirtishri Mishra, MD, declares that he has no conflict of interest. Laura Bukavina declares that she has no conflict of interest. Fredrick Schumacher, PhD, declares that he has no conflict of interest. Anna Quian, BS, declares that she has no conflict of interest. Christina Buzzy, PhD, declares that she has no conflict of interest. Carvell T. Nguyen, MD, PhD, declares that he has no conflict of interest. Vikas Gulani, MD, PhD, declares that he has no conflict of interest. Lee E. Ponsky, MD, declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Due to the retrospective nature of the study, informed consent was waived per IRB review protocol.

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