Original Article

Raised prostate-specific antigen alone may not be a true predictor in high-risk prostate cancer: A retrospective cohort analysis

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ABSTRACT

Introduction: Prostate-specific antigen (PSA) >20 ng/mL in isolation is a criterion for classification as "high-risk" prostate cancer (PCa). However, among Indian men, PSA elevation is often seen even in the absence of PCa and patients with PSA as the sole criterion for the high-risk disease may have different outcomes from those categorized as high risk due to adverse pathological features. We compared the operative, oncological, and functional outcomes after robot-assisted radical prostatectomy (RARP) in men with high-risk PCa categorized using PSA alone versus clinical and histopathological findings.

Materials and Methods: In an Institute Review Board-approved study, men undergoing RARP with high-risk PCa with at least 2-year follow-up were categorized into those with PSA >20 ng/ml being the sole criteria for being high risk (Group A) versus those with Gleason score ≥8 or ≥T2c disease but any PSA level (Group B). The two groups were compared for perioperative, oncological, and functional outcomes.

Results: Fifty-three patients with high-risk disease were included. Twenty-six patients (48.9%) were classified into Group A while 27 patients (50.9%) were classified into Group B. The median PSA was significantly higher in Group A (31 [26–35] ng/ml in Group A vs. 21 [12–34] ng/ml in Group B, $P = 0.006$) and on histopathology of radical prostatectomy specimen, 24 (92.3%) patients had GG ≤3 disease in Group A versus 10 (37%) patients in Group B ($P < 0.001$). Patients in both the groups had similar perioperative and continence outcomes. However, Group A had significantly lower biochemical recurrence rate (3/26 [11.5%]) as compared to Group B (11/27 [40.7%]) ($P = 0.012$).

Conclusions: PSA >20 ng/ml is the single most common criterion for stratification as high-risk PCa. However, men with PSA >20 ng/ml in isolation, without another adverse criterion, have better outcomes than men with adverse clinical or pathological criteria for high-risk disease.

INTRODUCTION

Prostate cancer (PCa) is among the most common noncutaneous malignancy in men accounting for more than 1 in every 5 new diagnoses of cancer in 2020.[1] Despite the high incidence, only a small proportion of patients die due to PCa. Accurate risk prediction tools must be developed since management decisions are based on risk stratification with a high-risk disease requiring aggressive treatment.[2] Pretreatment prostate-specific antigen (PSA), clinical tumor stage (T), and histopathological Gleason score (GS) have been identified as independent predictors for the prognosis of PCa.[3] In 1998, D'Amico *et al.* first proposed a three-group risk stratification system of PCa for predicting biochemical failure after radical prostatectomy (RP) and external beam radiotherapy, and this continues to be one of the most widely used clinical classification systems.[4] Over 20 predictive models including nomograms, probability graphs, and neural networks have been proposed, predominantly comprising these three factors.[5] Pretreatment PSA has

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been incorporated in all risk stratification systems, and PSA >20 ng/ml has been invariably labeled as a high-risk disease.[3,6-8]

A few studies have tried to address the substratification of high-risk disease based on several risk factors and assessed the prognostic role of individual PSA in this subgroup.[7,9] Based on PSA, the localized high-risk disease group offers two unique subsets – one with low PSA and high GS or T stage while the other with high PSA and low GS or T stage. Patients with low PSA and higher GS have higher cancer-specific mortality and poor response to androgen deprivation therapy.[10,11]

The importance of PSA-based risk stratification is particularly important in India. While it has been suggested that Indian men have lower age-specific PSA levels than their Western counterparts,[12] Indian men with lower urinary tract symptoms (LUTS) often have high PSA.[13] Further, cancer detection among Indian men with elevated PSA is lower than in Western populations,[14] and it has been proposed that the prevalence of chronic prostatitis may be a reason for higher PSA in this population where the biopsy has been performed primarily as an opportunistic screening among men with LUTS.[15]

Since management and prognosis depend on preoperative risk stratification, it becomes important to evaluate the outcomes of men with PSA alone being the criteria for high-risk stratification. We compared the operative, oncological, and functional outcomes in patients undergoing RARP for high-risk carcinoma prostate stratified using PSA alone (i.e., PSA >20 ng/ml) versus those with the clinical and histopathological reason for high-risk classification.

MATERIALS AND METHODS

In an Institute Review Board (IRB)-approved study (IRB number: IECPG-402/30.08.2018), all patients who underwent RARP at our institution between April 2005 and July 2018 and completed at least 2-year follow-up were retrospectively identified from hospital records. All patients were contacted and invited to visit the hospital for follow-up. If a patient had died, the time and cause of death were ascertained through records or a verbal autopsy, and these patients were excluded from the study. Patients were considered lost to follow-up if they could not be contacted or if no follow-up information was available. The patients' demographic as well as perioperative details were recorded. The prostate volume was recorded, as measured on preoperative ultrasonography. The preoperative PSA was used for risk stratification, and possible causes of fallacious rise in PSA including urinary instrumentation, prostatic massage, or urinary tract infection were excluded based on history or urine culture. The seventh edition of the American Joint Committee on Cancer tumor-lymph node-metastasis (TNM) classification was used to define the clinical stage, and histopathological grading was done according to the Gleason system. D'Amico classification was used for preoperative risk stratification.[4] The modified Vattikuti Institute prostatectomy technique was used in most cases, with some operated using the extraperitoneal and posterior first approaches.[16] Perioperative complications were recorded using the modified Clavien–Dindo scale.[17]

Patients with high-risk disease were included and categorized into those with PSA >20 ng/ml being the sole criteria for being high risk (Group A) versus those with GS ≥8 or ≥ T2c disease and any PSA (Group B). The two groups were compared for operative parameters, oncological and functional outcomes.

During the study-specific follow-up visit, information regarding biochemical recurrence and continence outcomes was obtained.[18] PSA >0.1 ng/ml at first follow-up (6 weeks after surgery) was defined as disease persistence.[19] Biochemical recurrence was defined as PSA >0.2 ng/ml. Survival outcomes (S) were recorded as patients treated with adjuvant therapies (Sx), patients without PSA recurrence (S0), and patients with PSA failure (S1).[18] Adjuvant therapies were defined as therapies, i.e., androgen deprivation therapy or radiation therapy within 90 days of surgery. Salvage therapies were defined as therapies offered at the time of biochemical recurrence (i.e., PSA failure).[19] Continence outcomes (C) were recorded as patients not using a pad (C0 – total continence), patients using one pad for security (C1), and patients using ≥1 pad (C2). Patients who were incontinent before surgery were marked Cx. For this study, we used social continence which was defined as the use of no pads or up to one safety pad (C0/C1) per day.[18] Most patients underwent nonnerve sparing resection because of high-risk disease, and hence, potency outcomes were not evaluated.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate. Categorical variables were compared using the Chi-square test, and continuous variables were compared using Student's *t*-test, multiple ANOVA, Mann–Whitney test, or Kruskal–Wallis test as appropriate. All statistical tests were two-sided. Statistical significance was taken as $P < 0.05$. Data were analyzed using IBM SPSS Statistics software (version 20.0, Chicago, IL, USA). The authors confirm the availability of and access to all data reported in this study.

RESULTS

181 patients who had completed 24 months post surgery and were willing for follow-up were included. Fifty-one patients (28.2%) had low-risk disease, 77 patients (42.5%)

patients had intermediate-risk disease, and 53 patients (29.3%) had high-risk disease. The 53 patients with high-risk disease were included in this study.

Among them, 26 patients (48.9%) were classified into Group A while 27 patients (50.9%) were classified into Group B. The mean age (±SD) of the study population was 65.1 (±6.2) years, and it was similar across both the groups [Table 1]. PSA was >20 ng/ml in 40/53 (75.4%) patients and was the most common individual risk factor for stratification into high risk category. The overall median (IQR) PSA was 28 (21–34), and it was significantly higher in Group A patients as compared to Group B (31 [26–35] ng/ml vs. 21 [12–34] ng/ml, $P = 0.006$)]. In Group B, 13 patients (48.1%) had PSA <20 ng/ml. Table 1 highlights the preoperative clinical stage, histopathological characteristics, and prostate volume.

The mean (SD) operative time was 185.3 (45.6) minutes, and the median blood loss was 250 (150–400) ml. Perioperative complications and the mean hospital stay were similar in the two groups [Table 2]. Table 2 also highlights the histopathological features on RP specimen. The grade group (GG) of the RP specimen was significantly different between the two groups. In Group A, 7 patients (26.9%) had GG 1 disease while 17 patients (65.4%) had GG 2–3. There were only 2 patients (7.7%) upgraded to the high-risk GS group (GG ≥ 4) on RP specimens. This highlights that 26.6% and 65.4% of the patients classified as high risk, merely based on PSA, had low- and intermediate-risk histopathology. Overall, 92.3% of the patients in Group A did not have high-risk disease pathology on RP specimen. In Group B, none of the patients had GG 1 disease on final histopathology. Ten patients (37%) had GG 2–3 disease while 17 patients (62.9%) patients had GG ≥4 disease.

The margin positivity rate was higher in Group B ($n = 10$, 37%) as compared to Group A ($n = 4$, 15.4%) but was not statistically significant ($P = 0.074$). Table 2 highlights the details of histopathological characteristics of RP specimen. Overall, seminal vesical invasion, extracapsular extension (ECE), perineural invasion, and lymph nodal involvement were statistically similar in both groups. Disease persistence after RP was found in 7 (13.2%) patients. Overall, 8 (15.1%) patients received adjuvant therapy (Sx) in the form of androgen deprivation or radiation, or both. The rates of disease persistence and adjuvant therapy were similar in both groups.

The median (IQR) follow-up of the study cohort was 91 (28–142) months. Among the oncological outcomes [Table 3], 15.1% received adjuvant therapy (Sx), and 26.4% of the patients had biochemical recurrence (S1) with the median (IQR) time of 18 (18–24) months. The patients with biochemical recurrence were significantly higher in Group B as compared to Group A (11 patients [40.7%] vs. 1 patient [11.5%], $P = 0.012$). The median time for BCR was similar in both groups.

Among the continence outcomes, overall 94.3% achieved social continence at 1 year. The early continence rate (at 6 weeks) and late continence rates (12 months) were similar in both groups. Table 3 highlights the oncological and continence outcomes in the study cohort.

DISCUSSION

We found that, among patients with high-risk PCa amenable for RP, 50% had PSA >20 ng/mL as the sole reason for the high-risk stratification and this group had better oncological outcomes after RP than patients who were classified as

Table 1: Comparison of preoperative parameters of patients with high-risk disease undergoing robot-assisted radical prostatectomy stratified as high risk based on raised prostate-specific antigen alone (Group A) versus stratified using histopathological or clinical characteristics (Group B)

Parameter	Overall (*n*=53)	Group A (*n*=26)	Group B (*n*=27)	*P*
Mean age (±SD), years	65.1 (±6.2)	64 (±6.5)	66.2 (±5.8)	0.374
Median PSA (IQR) ng/mL	28 (21–34)	31 (26–35)	21 (12–34)	0.006*
Mean prostate volume (±SD), cc	38.3 (±16.4) (*n*=40)	36.9 (±14.2) (*n*=22)	40.9 (±18.9) (*n*=18)	0.359
Preoperative clinical stage, *n* (%)				
cT1-T2a	34 (64.2)	23 (88.5)	11 (40.7)	<0.001*
cT2b	7 (13.2)	3 (11.5)	4 (14.8)	
≥T2c	12 (22.6)	0	12 (44.4)	
PSA category (ng/dl), *n* (%)				
<10	5 (9.4)	0	5 (18.5)	<0.001*
10-20	8 (15.1)	0	8 (29.6)	
>20	40 (75.5)	26 (100)	14 (51.9)	
Preoperative Gleason score, *n* (%)				
GS 3+3 (Grade Group 1)	10 (18.9)	10 (38.5)	0	0<0.001*
GS 3+4 (Grade Group 2)	17 (32.1)	10 (38.5)	7 (25.9)	
GS 4+3 (Grade Group 3)	7 (13.2)	6 (23.1)	1 (3.7)	
GS 4+4 (Grade Group 4)	16 (30.2)	0	16 (59.3)	
GS 4+5/5+4/5+5 (Grade Group 5)	3 (5.7)	0	3 (11.1)	

*$P<0.05$ is considered significant. PSA=Prostate-specific antigen, SD=Standard deviation, IQR=Interquartile range

Table 2: Comparison of perioperative parameters of patients with high-risk disease undergoing robot-assisted radical prostatectomy stratified as high risk based on raised prostate-specific antigen alone (Group A) versus stratified using histopathological or clinical characteristics (Group B)

Parameter	Overall (*n*=53)	Group A (*n*=26)	Group B (*n*=27)	*P*
Mean operative time (±SD), min	185.3 (±45.6)	188.3 (±45.9)	182.4 (±45.9)	0.644
Median blood loss (IQR), mL	250 (150–400)	300 (150–400)	200 (150–400)	0.501
Mean hospital stay (±SD), days	4.7 (±1.9)	5 (±1.9)	4.3 (±1.8)	0.180
Clavien–Dindo complications, *n* (%)				
Grade I	7 (13.2)	4 (15.4)	3 (11.1)	0.886
Grade II	2 (3.8)	1 (3.8)	1 (3.7)	
Grade III	2 (3.8)	1 (3.8)	1 (3.7)	
Grade IV	1 (1.9)	0	1 (3.7)	
Histopathological features on radical prostatectomy specimen				
Pathological tumor stage, *n* (%)				
pT2	26 (49.1)	16 (61.5)	10 (37)	0.093
pT3a	21 (39.6)	8 (30.8)	13 (48.1)	
pT3b	6 (11.3)	2 (7.7)	4 (14.8)	
Gleason score (grade group), *n* (%)				
GS 3+3 (Grade Group 1)	7 (13.2)	7 (26.9)	0	<0.001*
GS 3+4 (Grade Group 2)	15 (28.3)	11 (42.3)	4 (14.8)	
GS 4+3 (Grade Group 3)	12 (22.6)	6 (23.1)	6 (22.2)	
GS 4+4 (Grade Group 4)	14 (26.4)	2 (7.7)	12 (44.4)	
GS 4+5/5+4/5+5 (Grade Group 5)	5 (9.4)	0	5 (18.5)	
Margin positive, *n* (%)	14 (26.4)	4 (15.4)	10 (37)	0.074
ECE, *n* (%)	27 (50.9)	10 (38.5)	17 (63.0)	0.074
Seminal vesicle involvement, *n* (%)	6 (11.3)	2 (7.7)	4 (14.8)	0.413
Perineural invasion, *n* (%)	18 (34)	6 (23.1)	12 (44.4)	0.753
pN1 disease, *n* (%)	4 (7.5)	1 (3.8)	3 (11.1)	0.645
Mean number of lymph nodes removed (±SD), *n*	9.0 (±3.2)	8.9 (±3.1)	9.1 (±3.3)	0.884
Disease persistence, *n* (%)	7 (13.2)	2 (4.7)	5 (18.5)	0.426
Adjuvant therapy, *n* (%)	8 (15.1)	3 (11.5)	5 (18.5)	0.478

*$P<0.05$ is considered significant. PSA=Prostate-specific antigen, ECE=Extracapsular extension, IQR=Interquartile range, SD=Standard deviation

Table 3: Comparison of oncological and functional outcomes in patients with high-risk disease undergoing robot-assisted radical prostatectomy stratified as high risk based on raised prostate-specific antigen alone (Group A) versus stratified using histopathological or clinical characteristics (Group B)

Parameter	Overall (*n*=53), *n* (%)	Group A (*n*=26), *n* (%)	Group B (*n*=27), *n* (%)	*P*
Oncological outcomes (S)				
S0	31 (58.5)	20 (77)	11 (40.7)	0.012*
S1 (biochemical recurrence)	14 (26.4)	3 (11.5)	11 (40.7)	
SX	8 (15.1)	3 (11.5)	5 (18.5)	
Salvage therapy				
Androgen deprivation therapy	7 (13.2)	2 (7.7)	5 (18.5)	0.228
RT	3 (5.7)	0	3 (11.1)	
ADT + RT	4 (7.5)	1 (3.8)	3 (11.1)	
Site of biochemical recurrence				
Localized	3 (5.7)	0	3 (11.1)	0.538
Metastatic	4 (7.5)	2 (7.7)	2 (7.4)	
Local + metastatic	4 (7.5)	1 (3.8)	3 (11.1)	
Not known	3 (5.7)	0	3 (11.1)	
Continence outcomes (C)				
Social continence (C0/C1) at 6 weeks	16 (30.2)	10 (38.5)	6 (22.2)	0.198
Social continence (C0/C1) at 3 months	39 (73.6)	20 (76.9)	19 (70.4)	0.589
Social continence (C0/C1) at 6 months	48 (90.6)	24 (42.3)	24 (88.9)	0.670
Social continence (C0/C1) at 12 months	50 (94.3)	25 (96.2)	25 (92.6)	0.575

*$P<0.05$ is considered significant. ADT=Androgen deprivation therapy, RT=Radiation therapy

high risk due to adverse clinical or pathological features. Among the three criteria for classifying PCa as high risk, PSA >20 ng/mL alone is the most common factor for high-risk stratification, both in the Western and Indian populations. In a multi-institutional European study involving high-risk PCa patients with PSA >20 ng/ml, 48.5% had only high PSA as a sole factor for high-risk stratification.[9] Similar results were reported in an Indian population.[20]

PSA varies with race, genetic differences, and diet factors, thereby causing significant differences in positive predictive value for cancer.[21,22] Studies among Indian men have noted lower PSA levels among the general population. This should mean that the traditional cutoff of 4 ng/mL is abnormally high among Indian men and the cancer detection rate should be higher than in Western populations.[12] On the contrary, even with the existing trigger of 4 ng/mL for a

biopsy, cancer detection rates in Indian men are lower than in the Western population, and it is suggested that the trigger PSA should be higher in Indians.[15] A possible explanation for this dichotomy in the existing data would be that Indian men with LUTS and BPH have a high PSA.[14] This would suggest that there are conditions other than PCa that cause PSA to rise among men with LUTS and BPH in India. Among 4702 patients undergoing evaluation of LUTS, Agnihotri *et al*. found that 29.9% had PSA >4 ng/ml. For PSA 4–10 ng/ml, the cancer detection rate was 15% compared to 32% in the Western population.[13] They proposed raising the PSA trigger for biopsy to 5.82 ng/ml in Indian men. Similarly, Agarwal *et al*.[14] found a higher median PSA and proposed a cutoff of 6 ng/ml for the highest sensitivity and specificity for PCa detection. In another study of 1090 Indian men with BPH, 8.2% of the patients had PSA >10 ng/ml as compared to 2%–3% in Western populations.[23] India does not have a PSA screening policy, and most men get a PSA test through opportunistic screening while seeking treatment for LUTS. The above data suggest that nonmalignant causes may be contributing to their high PSA and relying on PSA alone to stratify those detected with PCa as high-risk may not be appropriate.

High PSA is often associated with higher stages and grades of disease. Lojanapiwat *et al*.[24] reported a significant correlation of PSA with PCa diagnosis, bone metastasis, and GS >7 disease in 1116 Asian patients undergoing prostate biopsy and 395 patients diagnosed with PCa. However, there may not be a linear correlation between PSA and PCSM as Izumi *et al*. found that once PSA is > 100 ng/ml, it no longer has a prognostic role for overall survival or PCSM.[25] Mahal *et al*. studied PCa-specific mortality (PCSM) in patients with low PSA but high-grade PCa.[10] Among 494,793 patients from the National Cancer Database and 136,113 patients from the Surveillance, Epidemiology, and End Results program with the cT1-4N0M0 disease, they found high PCSM even in patients with PSA ≤2.5 ng/ml, suggesting that the PSA may not always be elevated in men with high PCSM. Gallina *et al*. reported the poor predictive value of PSA >20 ng/ml alone for the pathological stage of PCa in 5193 patients undergoing RP and found predictive accuracy of 63.6% for extracapsular extension, 63.7% for seminal vesicle invasion, and 70.6% for lymph nodal involvement.[26]

These studies stress the fact that high PSA alone does not essentially predict unfavorable outcomes on histopathology or survival. In terms of survival, Yossepowitch *et al*. demonstrated that 10-year PCSM was significantly higher (9%) in patients with a PSA >20 ng/ml when compared with those having PSA <20 ng/ml (3%).[6] Similarly, Stephenson *et al*. also reported significantly higher 15-year PCSM in patients with PSA >20 ng/ml.[7] These studies suggest that a PSA >20 ng/ml in isolation is an independent high-risk factor for PCa mortality. On the contrary, Zwergel *et al*. retrospectively analyzed 275 patients of PCa undergoing RP with preoperative PSA >20 ng/ml and reported 10-year disease-specific survival of 83%. Furthermore, they did not find preoperative PSA as an independent prognostic marker for tumor-specific survival.[27]

Spahn *et al*.[9] assessed the role of individual high-risk factors in a multi-institutional European study of 712 patients with high-risk PCa undergoing RP between 1987 and 2005. They divided the cohort into four risk groups: Group 1: PSA >20 ng/ml, Group 2: PSA >20 ng/ml+ >cT2 disease, Group 3: PSA >20 ng/ml + biopsy GS >7, and Group 4: PSA > 20 ng/ml+ >cT2 disease + biopsy GS >7. They identified high heterogeneity among the high-risk PCa, and Group 1 had around 95% of GS ≤7 disease with significantly higher pathologic stage 2 (pT2) disease (33%), negative surgical margins (54%), and negative lymph nodes (85%) as compared to other groups. The 10-year cancer-specific survival (89%) was significantly higher than other risk groups, and the authors concluded that patients with PSA >20 ng/ml form a heterogeneous group and an elevated PSA in isolation was not sufficient to define a patient as high risk. The clinical stage and GS along with PSA allow better risk stratification. A higher number of risk factors at diagnosis were significantly correlated to unfavorable pathology and clinical progression.

A few studies from the Indian subcontinent have tried to assess the outcomes of RP in high-risk patients of localized PCa. Kulkarni *et al*.[28] reported outcomes of 208 patients with high-risk PCa undergoing RP from 1996 to 2010 and could not find a significant association of preoperative PSA with the pathological staging or cancer survival. They reported pathological stage as an independent predictor of biochemical recurrence-free survival and pathological grade as an independent predictor of metastasis-free survival. In another study, Gupta *et al*.[20] studied 90 patients of high-risk PCa undergoing RARP from July 2010 to January 2015 and found PSA > 20 ng/ml as the most common factor for high-risk stratification. They also reported a 20% margin positivity rate, 40% pT3a disease, and 10% lymph nodal involvement. These findings were reiterated in our study. They did not analyze the prognostic role of PSA >20 ng/ml alone. Our study analyzed a specific question of prognostic effect PSA >20 ng/ml in isolation, which appears to be the most common risk factor for high-risk stratification.

Our study is among the few contemporary studies trying to assess the role of PSA >20 ng/ml in patients of high-risk localized PCa undergoing RARP in this region with a median follow-up of over 7 years. However, the study has limitations. Due to the limited sample size, we could not stratify the population further into various combinations of individual high-risk factors. Only 181 patients could be followed up leading to attrition bias. Since only the patients who lived and followed up were included, the survival analysis and Kaplan–Meier estimation could not be

done. The pathology specimens could not be reviewed by a single genitourinary pathologist; however, all the reporting was done by experienced genitourinary pathologists. The percentage of positive cores on biopsy was not available for all patients and hence was not included for risk stratification. We did not divide the cohort based on number of high-risk factors, owing to a small sample size, and this may have led to bias in the study. PSA testing was not done from the same institutional laboratory, but reporting was done from standard laboratories, and the lowest of the available preoperative PSA was taken for risk stratification. The rate of adjuvant therapy in our series is low because of variable practice patterns at various time points, surgeons' discretion, and patients' compliance over the study period of 13 years. Two important concerns for high PSA with low-intermediate grade disease are prostate volume and evidence of inflammation. The prostate volume, which could impact PSA, was available for 40/53 (75.4%) patients. However, it was similar in both groups and hence tends to have minimal impact on PSA. As the pathology slides could not be re-reviewed, the degree of associated inflammation or coexistent chronic prostatitis could not be studied.

CONCLUSIONS

High-risk PCa is a heterogeneous group with PSA >20 ng/ml being the most common factor for stratification as high risk. Patients with PSA >20 ng/ml being the sole risk factor have better oncological outcomes than those with GS >7 or T > T2b disease as the risk factors. This is important in patient counseling and management, and larger studies on PSA variability and outcomes are required to clearly identify the role of PSA in risk stratification.

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