Research Article

Prostatic Acid Phosphatase (PAP) Predicts Prostate Cancer Progress in a Population-Based Study: The Renewal of PAP?

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Objective. To characterize the disease progression and median survival of patients with prostate cancer (PCa) according to the prostatic-specific acid phosphatase (PAP) analysis in a population-based study from the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods. Prostate cancer patients with completed PAP results were identified using the SEER database of the National Cancer Institute. The Mann-Whitney Sum test was utilized to compare the statistical significance for measurement data and ranked data. Data were stratified by ages, races, TNM Classification of Malignant Tumors (TNM), pathological grades, number of tumors, PAP, and survival duration. Multivariable logistic analysis was performed to identify predictors of the presence of invasion and metastases. Cox regression was analyzed for the factors associated with all-cause mortality and prostate cancer-specific mortality. Moreover, survival curve was used to detect the survival months. The unknown data were excluded from these tests. Results. In total, there are 5184 PAP+ patients and 3161 PAP- patients involved. The Mann-Whitney Sum test showed that slightly greater tumor size ($P = 0.03$), elevated lymphatic ($P = 0.005$) and distant ($P < 0.001$) metastasis rate, higher pathological grade ($P < 0.001$), localized tumor number ($P < 0.001$), and shortened survival months ($P < 0.001$) were observed in the PAP+ group compared with the PAP- group. In the multivariable logistic regression, invasion and metastasis Hazard Ratio (HR) were elevated significantly ($P < 0.001$) in the PAP+ individuals. In the survival analysis, PAP- patients experienced the prolonged median survival. In the postsurgical patients, the survival months were still longer in PAP+ patients compared with the negative ones ($P < 0.001$), though surgery prolonged the survival months of both groups. Survival months stratified by localized, invasion, and metastasis situations were analyzed. In the three stratified subgroups, the survival duration is significantly decreased in the PAP+ individuals in the localized PCa group ($P < 0.001$) and the metastasis group ($P = 0.013$). Conclusions. The findings of this study provide population-based estimates of the PCa progress and prognosis for patients with different PAP results, which may suggest a renewed period for the PAP.

1. Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer with the fifth mortality in the males [1]. Screening markers, prostate-specific antigen (PSA) included, can result in the early detection of the disease [2]. Nevertheless, the predictive function of this biomarker for the PCa progress is still limited. Robust population-based estimates relating to the progress of PCa, including the metastases, localized tumor numbers, tumor sizes, survival years, and cancer-specific survival (CSS), at PCa are lacking, partly due to the single widely used evaluated index in the clinic.

Human prostatic-specific acid phosphatase (PAP) is a secreted glycoprotein with the molecular weight of 100 kDa synthesized in lysosomes of prostate epithelial cells [3]. It has been determined to be associated with the weight of prostate tissue [4]. There are two forms of PAP, including the cellular form (cPAP, highly expressed in the prostate cells) and the secretory form (sPAP, expressed only in the prostate and is mostly released into seminal fluid) [5], with different
isolectric points and molecular weights [6]. Some reported that different mRNA was encoded in the different forms of PAP and the physiologic substrate is still needed to be studied [6]. The PAP is increased in the circulation of PCa patients while its prostate expression is reduced. As is claimed, cPAP has a growth-suppressing effect while its prostate expression is reduced. The PAP is increased in the circulation of PCa patients [6]. The PAP is increased in the circulation of PCa patients [6]. The SEER database includes information on cancer, which is from the National Cancer Institute (NCI) in the United States (US), for 28% of the US population. In this research, patient information during 1998-2003 was analyzed, during which period the PAP was used as the screening method for PCa and after 2003, PAP is not registered in the SEER database since then.

2. Materials and Methods

2.1. Population Source. The current study comprised SEER-related data. The SEER database includes information on cancer, which is from the National Cancer Institute (NCI) in the United States (US), for 28% of the US population. In this research, patient information during 1998-2003 was analyzed, during which period the PAP was used as the screening method for PCa and after 2003, PAP is not registered in the SEER database since then.

2.2. Study Population. Within the SEER database, we identified 5184 PAP-positive (PAP+) individuals and 3161 PAP-negative (PAP−) individuals diagnosed with prostate cancer (International Classification of Diseases (ICD)). For each subgroup, the following were excluded: individuals with unknown race (n = 65), TNM stages (n for T = 3067, n for N = 1866, and n for M = 249), invasive situation (n = 259), grade (n = 523), and follow-up survival months (n = 763), which process is shown in Figure 1.

2.3. Covariates. For each subject, at age at diagnosis (30-50, 51-70, 71-85, and ≥86), races (white, black, Asian, and American Indian), tumor size (T1-4), lymphatic metastases (N0 and N1-3), distant metastases (M0 and M1), invasive status (localized tumor, invasive tumor, and metastasis tumor), pathological grade (grade1-4), and number of localized tumors were assigned. Moreover, the following were also analyzed: survival months, prostate cancer-specific survival months, and survival months for the surgical patients. The invasion status was determined by SEER Extent of Disease Codes and Coding Instructions 3rd edition. The survival duration was analyzed only for the completed data with the exact endpoint. Surgery status was according to the “Reason no cancer-directed surgery” section. PAP data was gotten from the “tumor marker 1” of the prostate cancer and exact definition was referenced in SEER Self Instructional Manual.
the shortened survival months (144.0 (95.0-168.0) vs. 152.0
the PAP- individuals (\textit{patients presented lymphatic metastases more often than
Table 1. The Mann-Whitney Sum test showed that PAP+
characteristics of the study cohort are also presented in
Table 1. The Mann-Whitney Sum test showed that PAP+
patients presented lymphatic metastases more often than
in the logistic regression model described. In the Cox regres-
model, enter method was used. All tests were two-sided,
with a significance level set at \( \star P \leq 0.05 \) and \( \star \star P \leq 0.01 \).

3. Results
The flow diagram for this analysis was shown in Figure 1. The total PAP+ patient number is 5184 and the PAP-
num-er is 3161. After the exclusion, the exact number of each
The total PAP+ patient number is 5184 and the PAP- num-
ber is 3161. After the exclusion, the exact number of each
group (\( \star\star P < 0.001 \)), elevated pathological grade in the
Table 2. The pathological grade and the number of localized
tumors were significantly related to the metastasis situation
\( \star\star P < 0.001 \). In PAP+ group, invasion (1.78(1.39-2.26))
and metastasis (3.03 (2.49-3.70)) Hazard Ratio (HR) were
increased in the PCa-specific mortality group (vs. PAP-;
HR, 2.87 (2.48-3.32); \( \star\star P < 0.001 \)). For the surgery treatment
in PCa-specific mortality group, no significant changes were
observed (vs. nonsurgery; HR, 1.09 (0.91-1.30); \( P = 0.36 \).

In the survival curve analysis, the median survival
among the entire cohort was 136 (69-163) months, with
patients with PAP negative subtype experiencing the pro-
longed median survival (143 (87-167)). In the postsurgical
patients, the survival months were still longer in PAP-
patients (144 (95-168) vs. 152 (126-172), \( \star\star P < 0.001 \)). The
overall survival estimates (Figure 2(a)), as stratified by PAP
subtype (Figure 2(b)), and the PAP effect on the survival
months after surgical treatment (Figure 2(c)) are graphically
displayed in Figure 2. The surgery effect on the survival
months in the PAP-positive patients was also studied in
Figure 2(d) which showed that surgery prolonged the sur-
vival months of the PAP-positive individuals (95 (144-168)
vs. 48 (118-156), \( \star\star P < 0.001 \)).

Survival months stratified by localized, invasion and
metastasis situations were analyzed in Figure 3(a). In the
three stratified subgroups (shown in Figures 3(b)–3(d)), the
survival duration is significantly decreased in the PAP+
individuals in the localized PCa group (86 (140-164) vs. 99
(146-168), \( \star\star P < 0.001 \)) and the metastasis group (7 (19-46)
vs. 8 (26-69), \( P = 0.013 \)).

4. Discussion
Prostate cancer screening has been widespread using PSA
since 1990s. After that time, PAP was used less and less in
the clinical work. This was because PSA was more sensitive
than PAP in the serum detection and screening of prostate
cancer. The use of PSA, however, also leads to overdiagnosis
and overtreatment of prostate cancer. Moreover, it is not
effective to use in the prediction of the metastases and the
prognosis, especially the prognosis after surgery. In this
study, the SEER database was used to analyze the predictive
effect of PAP on the PCa prognosis and the disease progress.
We found that patients with PAP-positive subtype showed
easier metastases, larger tumor size, more localized tumor
numbers, higher pathological grade, and shortened survival
duration. Moreover, the PAP-positive patients also present
decreased survival months even after the surgical treatment.
Though it is already suggested that PAP is one of the
important markers for the test of the prognosis and the
PCa progress, it is still lacking the population-based sur-
vival outcomes and disease progress, to our knowledge.
Moreover, the details of PCa progression and prognosis
were firstly present in this analysis.
PAP was first reported by Gutman in 1938 that the increased levels of serum PAP was observed in patients with metastatic prostate cancer [12]. Shortly thereafter, it is established that PAP is a tumor marker for PCa. It is also suggested that elevated PAP should be paid great attention to though maybe no clinical evidence of metastasis happens.

### Table 1: Incidence proportion and median of patients with PAP-positive (PAP+) and PAP-negative (PAP-).

| Age at diagnosis (y) | PAP+ median (IQR) | No. (%) | PAP- median (IQR) | No. (%) | Total | P value |
|----------------------|-------------------|---------|-------------------|---------|-------|---------|
| 30-50                | 48 (45-50)        | 161, 3.11 | 48 (46-50)        | 131, 4.14 | 292 | 0.365 |
| 51-70                | 63 (58-67)        | 2857, 55.11 | 63 (58-67)        | 1927, 60.96 | 4784 | 0.968 |
| 71-85                | 76 (73-79)        | 1972, 38.04 | 76 (73-78)        | 1037, 32.81 | 3009 | *0.025 |
| ≥86                  | 88.5 (87-91)      | 194, 3.74 | 88 (87-90)        | 66, 2.09 | 260 | 0.071 |
| Total                |                   | 5184, 100 |                   | 3161, 100 | 8345 |         |

| Race                 | PAP+ No. (%)     | PAP- No. (%) | Total No. (%) | P value |
|----------------------|-----------------|--------------|---------------|---------|
| White                | NA              | 3838, 74.73  | NA            |         |
| Black                | NA              | 1021, 19.88  | NA            |         |
| Asian                | NA              | 259, 5.04    | NA            |         |
| American Indian      | NA              | 18, 0.35     | NA            |         |
| Total                | NA              | 5136, 100    | NA            |         |

| T                    | PAP+ No. (%)     | PAP- No. (%) | Total No. (%) | P value |
|----------------------|-----------------|--------------|---------------|---------|
| T1                   | NA              | 1362, 42.30  | NA            | *0.03   |
| T2                   | NA              | 1229, 38.17  | NA            | 2084    |
| T3                   | NA              | 440, 13.66   | NA            | 737     |
| T4                   | NA              | 189, 5.87    | NA            | 304     |
| Total                | NA              | 3220, 100    | NA            | 5280    |

| N                    | PAP+ No. (%)     | PAP- No. (%) | Total No. (%) | P value |
|----------------------|-----------------|--------------|---------------|---------|
| N0                   | NA              | 3804, 98.81  | NA            | 6409    | **0.005 |
| N1-3                 | NA              | 46, 1.19     | NA            | 38      |
| Total                | NA              | 3850, 100    | NA            | 6479    |

| M                    | PAP+ No. (%)     | PAP- No. (%) | Total No. (%) | P value |
|----------------------|-----------------|--------------|---------------|---------|
| M0                   | NA              | 4450, 89.07  | NA            | 7424    | **<0.001|
| M1                   | NA              | 546, 10.93   | NA            | 672     |
| Total                | NA              | 4996, 100    | NA            | 8096    |

| Invasion             | PAP+ No. (%)     | PAP- No. (%) | Total No. (%) | P value |
|----------------------|-----------------|--------------|---------------|---------|
| No invasion          | NA              | 4185, 3.92   | NA            | 7063    | **<0.001|
| Invasion beyond capsule | NA         | 242, 4.85    | NA            | 336     |
| Distant metastasis   | NA              | 560, 11.23   | NA            | 687     |
| Total                | NA              | 4987, 100    | NA            | 8086    |

| Grade                | PAP+ No. (%)     | PAP- No. (%) | Total No. (%) | P value |
|----------------------|-----------------|--------------|---------------|---------|
| 1                    | NA              | 174, 3.66    | NA            | 317     |
| 2                    | NA              | 3052, 64.23  | NA            | 5249    | **<0.001|
| 3                    | NA              | 1498, 31.52  | NA            | 2209    |
| 4                    | NA              | 28, 0.59     | NA            | 47      |
| Total                | NA              | 4752, 100    | NA            | 7822    |

| Number of localized tumors | PAP+ No. (%) | PAP- No. (%) | Total No. (%) | P value |
|---------------------------|--------------|--------------|---------------|---------|
| 1.0 (1.0-1.0)             | 5184, 100    | 1.0 (1.0-2.0) | 3161, 100    | 8345    | **<0.001|

| Survival months (all-cause) | PAP+ No. (%) | PAP- No. (%) | Total No. (%) | P value |
|-----------------------------|--------------|--------------|---------------|---------|
| 134.0 (63.0-161.0)          | 4761, 100    | 143.0 (88.0-166.0) | 2821, 100    | 7582    | **<0.001|

| Survival months (prostate cancer-specific) | PAP+ No. (%) | PAP- No. (%) | Total No. (%) | P value |
|---------------------------------------------|--------------|--------------|---------------|---------|
| 47.00 (16.00-90.00)                         | 963, 100     | 93.00 (52.75-132.00) | 962, 100     | 1925    | **<0.001|

| Survival months (postsurgical) | PAP+ No. (%) | PAP- No. (%) | Total No. (%) | P value |
|---------------------------------|--------------|--------------|---------------|---------|
| 144.0 (95.0-168.0)             | 1642, 100    | 152.0 (125.8-172.0) | 1118, 100    | 2760    | <0.001 |

To value the PAP+/- ratio of each subgroups, the total effective patient number of each group is calculated. As the data were measurement data and ranked data, the Mann-Whitney Sum test was utilized. Abbreviations: + denotes positive; − denotes negative; PAP: prostatic acid phosphatase; TNM: tumor-node-metastasis; No.: number; %: percent; *P ≤ 0.05; **P ≤ 0.01.
Table 2: The multivariable logistic regression analysis for the presence of metastases at diagnosis of prostate cancer.

| Age at diagnosis (y) | Localized | Race | Grade | Number of localized tumors | PAP | The multivariable logistic regression analysis Hazard Ratio (95% CI) | Among pt. with invasion | Among pt. with metastasis |
|----------------------|-----------|------|-------|-----------------------------|-----|--------------------------------------------------------------------|------------------------|--------------------------|
| 25-50                | 256       | 13   | 2      | 1 (Reference)               | NA  | 1 (Reference)                                                      | 1.00 (0.61-1.68)       | NA                       |
| 51-70                | 4217      | 185  | 185    | 1 (Reference)               | NA  | 1 (Reference)                                                      | 1.01 (0.56-1.81)       | NA                       |
| 71-85                | 2438      | 125  | 335    | 1.06 (0.76-1.37)            | NA  | 1 (Reference)                                                      | 1.07 (0.68-1.70)       | NA                       |
| ≥86                  | 152       | 13   | 62     | 1.00 (0.76-1.37)            | NA  | 1 (Reference)                                                      | 1.00 (0.61-1.68)       | NA                       |
| Race                 |           |      |       |                             |     |                                                                     |                        |                          |
| White                | 5303      | 238  | 478    | 1 (Reference)               | NA  | 1 (Reference)                                                      | 1.00 (0.61-1.68)       | NA                       |
| Black                | 1184      | 79   | 157    | 1.49 (1.14-1.93)            | NA  | 1.47 (1.22-1.78)                                                  | 1.49 (1.22-1.78)       | NA                       |
| Asian                | 495       | 15   | 42     | 0.68 (0.40-1.15)            | NA  | 0.68 (0.40-1.15)                                                  | 0.68 (0.40-1.15)       | NA                       |
| American Indian      | 21        | 4    | 8      | 4.24 (1.45-12.46)           | NA  | 4.23 (1.46-12.46)                                                 | 4.23 (1.46-12.46)      | NA                       |
| Grade                |           |      |       |                             |     |                                                                     |                        |                          |
| 1                    | 299       | 6    | 6      | 1 (Reference)               | NA  | 1 (Reference)                                                      | 1.00 (0.61-1.68)       | NA                       |
| 2                    | 4880      | 139  | 185    | 1.42 (0.62-3.24)            | NA  | 1.42 (0.62-3.24)                                                  | 1.42 (0.62-3.24)       | NA                       |
| 3                    | 1699      | 173  | 315    | 5.20 (2.31-11.99)           | NA  | 5.20 (2.31-11.99)                                                 | 5.20 (2.31-11.99)      | NA                       |
| ≥4                   | 26        | 3    | 16     | 5.75 (1.36-24.35)           | NA  | 5.75 (1.36-24.35)                                                 | 5.75 (1.36-24.35)      | NA                       |
| Number of localized tumors | 6218     | 304  | 648    | 1 (Reference)               | NA  | 1 (Reference)                                                      | 1.00 (0.61-1.68)       | NA                       |
| PAP                  |           |      |       |                             |     |                                                                     |                        |                          |
| ≥2                   | 815       | 32   | 39     | 0.81 (0.61-1.07)            | NA  | 0.81 (0.61-1.07)                                                  | 0.81 (0.61-1.07)       | NA                       |
| <2                   | 2878      | 127  | 500    | 1 (Reference)               | NA  | 1 (Reference)                                                      | 1.00 (0.61-1.68)       | NA                       |

The multivariable logistic regression analysis was used to determine whether age and race were associated with the presence of metastases at diagnosis of prostate cancer. Other variables included in the model included pathological grade and number of localized tumors. The likelihood ratio test (LRT) is used in the multivariable logistic regression analysis. Abbreviations: PAP: prostate acid phosphatase; P: p-value; *P ≤ 0.05; **P ≤ 0.01.
Table 3: The multivariable Cox regression for all-cause mortality and prostate cancer-specific mortality among PCa patients and postsurgical dead.

| Age at diagnosis (y) | All-cause mortality | Prostate cancer-specific mortality |
|----------------------|----------------------|----------------------------------|
| Pt. no.              | Hazard Ratio (95% CI) | P value | Pt. no.              | Hazard Ratio (95% CI) | P value |
| 30-50                | 292                  | 1 (Reference) | NA                  | 285                  | 1 (Reference) | NA |
| 51-70                | 4784                 | 2.88 (1.84-4.51) | **<0.01 | 4487                 | 2.16 (1.24-3.77) | **<0.01 |
| 71-85                | 3009                 | 7.57 (4.82-11.89) | **<0.01 | 2662                 | 6.09 (3.47-10.69) | **<0.01 |
| ≥86                  | 260                  | 23.43 (14.17-38.73) | **<0.01 | 228                  | 17.34 (8.63-34.83) | **<0.01 |

Race

| Race                | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|---------------------|---------|-----------------------|---------|---------|-----------------------|---------|
| White               | 6209    | 1 (Reference)         | NA      | 5649    | 1 (Reference)         | NA      |
| Black               | 1473    | 1.33 (1.17-1.50)      | **<0.01 | 1386    | 1.46 (1.20-1.77)      | **<0.01 |
| Asian               | 563     | 0.85 (0.72-1.01)      | 0.06    | 529     | 0.81 (0.63-1.05)      | 0.11    |
| American Indian     | 35      | 2.00 (0.64-6.27)      | 0.24    | 34      | 1.25 (0.17-9.05)      | 0.82    |

T

| T       | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|---------|---------|-----------------------|---------|---------|-----------------------|---------|
| T1      | 2153    | 1 (Reference)         | NA      | 1954    | 1 (Reference)         | NA      |
| T2      | 2084    | 0.95 (0.86-1.05)      | 0.31    | 1927    | 0.96 (0.82-1.13)      | 0.64    |
| T3      | 737     | 0.59 (0.48-0.72)      | **<0.01 | 692     | 0.66 (0.49-0.89)      | **<0.01 |
| T4      | 304     | 0.98 (0.76-1.26)      | 0.88    | 276     | 0.87 (0.59-1.28)      | 0.49    |

N

| N       | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|---------|---------|-----------------------|---------|---------|-----------------------|---------|
| N0      | 6409    | 1 (Reference)         | NA      | 5898    | 1 (Reference)         | NA      |
| N1      | 38      | 2.85 (1.68-4.85)      | **<0.01 | 36      | 5.01 (2.65-9.46)      | **<0.01 |
| N2      | 27      | 1.50 (0.80-2.83)      | 0.21    | 25      | 3.10 (1.45-6.65)      | **<0.01 |
| N3      | 5       | 3.82 (1.41-10.32)     | **<0.01 | 5       | 2.29 (0.32-16.53)     | 0.41    |

M

| M       | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|---------|---------|-----------------------|---------|---------|-----------------------|---------|
| M0      | 7424    | NA                    | NA      | 6857    | NA                    | NA      |
| M1      | 672     | NA                    | NA      | 590     | NA                    | NA      |

Grade

| Grade   | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|---------|---------|-----------------------|---------|---------|-----------------------|---------|
| 1       | 317     | 1 (Reference)         | NA      | 281     | 1 (Reference)         | NA      |
| 2       | 5249    | 0.79 (0.65-0.96)      | *0.02   | 4847    | 0.81 (0.60-1.10)      | 0.18    |
| 3       | 2209    | 1.20 (0.98-1.48)      | 0.08    | 2025    | 1.41 (1.03-1.92)      | *0.03   |
| 4       | 47      | 2.39 (1.20-4.73)      | **<0.01 | 39      | 2.35 (0.83-6.68)      | 0.11    |

Number of localized tumors

| Number of localized tumors | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|----------------------------|---------|-----------------------|---------|---------|-----------------------|---------|
| 1                          | 6475    | 1 (Reference)         | NA      | 6475    | 1 (Reference)         | NA      |
| ≥2                         | 1870    | 1.88 (1.71-2.06)      | **<0.01 | 1187    | 1.89 (1.62-2.21)      | **<0.01 |

Location

| Location       | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|----------------|---------|-----------------------|---------|---------|-----------------------|---------|
| Localized      | 7063    | 1 (Reference)         | NA      | 652     | 1 (Reference)         | NA      |
| Invasion       | 336     | 2.09 (1.64-2.66)      | **<0.01 | 1 311   | 2.21 (1.54-3.18)      | **<0.01 |
| Metastasis     | 687     | 6.48 (3.42-12.30)     | **<0.01 | 606     | 9.52 (4.47-20.24)     | **<0.01 |

PAP

| PAP | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|-----|---------|-----------------------|---------|---------|-----------------------|---------|
| -   | 3161    | 1 (Reference)         | NA      | 2879    | 1 (Reference)         | NA      |
| +   | 5184    | 1.04 (0.95-1.14)      | 0.42    | 4783    | 2.87 (2.48-3.32)      | **<0.01 |

Surgery

| Surgery | Pt. no. | Hazard Ratio (95% CI) | P value | Pt. no. | Hazard Ratio (95% CI) | P value |
|---------|---------|-----------------------|---------|---------|-----------------------|---------|
| Y       | 2760    | 1 (Reference)         | NA      | 2553    | 1 (Reference)         | NA      |
| N       | 5585    | 1.12 (1.00-1.26)      | *0.05   | 5109    | 1.09 (0.91-1.30)      | 0.36    |

The multivariable Cox regression was performed to identify covariates associated with increased all-cause mortality using the same variables as in the logistic regression model described. In the Cox regression model, enter method was used. Abbreviations: Pt. no.: patient number; y: years; TNM: tumor-node-metastasis; Y: yes; N: no; *P ≤ 0.05; **P ≤ 0.01.
Moreover, in the following years, the investigators reported that survival duration was significantly shortened for patients with elevated serum PAP [15], which is not completely consistent with this research. In the cancer of other tissues, small intestine, pancreas, and bladder included, PAP may also lead to an increased level. Thus, the slight elevation of PAP may reflect cancers other than the prostate [15, 16]. In the cancer-specific survival (CSS) study, it is showed that when PAP concentration is <1.5 U/L, 1.5-2.4 U/L, and >2.5 U/L, the progression of prostate cancer is 93%, 87%, and 75% (P = 0.013), respectively, which shows better than the PSA test (<10 ng/mL, 10-20 ng/mL, and >20 ng/mL, progression of prostate cancer is 92%, 76%, and 83%, P = 0.393, respectively). However, the CSS study is only involved in 193 patients [17]. In this study, CSS is also analyzed based on a population-based study. However, PAP is still not sensitive for the early stage diagnosis of the PCa and PSA was first isolated in seminal plasma in 1971 and widely used as a screening marker since 1990s.

Although PSA has largely replaced PAP as an early-stage screening marker, PAP is still an important prognostic marker in advanced and metastatic PCa [18]. It has been reported that secretory PAP (sPAP) in osteoblastic bone metastases stimulated collagen synthesis and alkaline phosphatase expression of bone cells [18]. After that, it was demonstrated not only for the elevation of sPAP in advanced PCa but also the cellular PAP (cPAP) expression is also highly expressed in human PCa bone metastases and stimulates preosteoblastic proliferation and differentiation [19]. It is also reported that PAP derived from PCa cells directly stimulates bone mineralization [16]. Recently, as is known, PAP secreted by PCa cells in osteoblastic bone metastases increases the RANK/RANKL/OPG system and plays a critical role in the vicious interaction between cancer and bone cells. Thus, the inhibition of sPAP may be a choice for PCa osteoblastic bone lesions [10]. Interestingly, it is reported that 88% of castration-resistant PCa (CRPC) bone metastases express prostatic acid phosphatase (PAP) in bone metastasis.
and there exists no significant difference between the osteoblastic and osteolytic lesions [16]. This may be due to the various kinds of factors involved in the osteolytic lesions. While PAP appears to drive the osteoblastic response, it can be moderated or negated by the other osteolytic factors in the microenvironment.

It is noteworthy that PAP is treated as a useful antigen for prostate cancer therapy. The vaccine treatment, sipuleucel-T, is used in clinic work. It is also the first vaccine for cancer treatment. This FDA-approved therapy is based on the idea that over 95% of prostate cancer cells express PAP specifically [20]. PAP is used to be fused with granulocyte-macrophage colony-stimulating factor (GM-CSF) thus presented to antigen-presenting cells (APCs) which are collected from the patient. These activated APCs are then introduced to the patient for induction of T cells in vivo and T cells are activated and attack prostate cancer cells in patients [15]. This vaccine treatment resulted in a 4.1-month longer median overall survival compared with placebo with a reduction in the risk of death [21].

Because of these recent applications of PAP, the PAP study returns to the view in the clinic work. In this study, PAP-positive patients present the higher metastasis rates, the larger tumor sizes, more localized tumor numbers, and higher pathological grade. The survival duration is also shortened in the PAP-positive group as was reported previously, which suggests a prognosis effect of PAP towards PCa. Interestingly, it is the first time to observe that the survival duration is still decreased in the PAP-positive group even after the surgery treatment. In this way, whether other treatment should be used before surgery for the PAP-positive individuals is still worth studying. Moreover, PAP is argued to be a good choice for the prognosis caused by PCa specifically but not other lethal factors, as is resulted from the COX regression study. Some even reported that the elevated serum pretreatment PAP levels were considered to

**Figure 3**
be a relative contraindication to surgery [14, 18]. In our study, however, the survival months of surgical patients is still longer even in the PAP-positive group (95 (144-168) vs. 48 (118-156), \( P < 0.001 \), shown in Figure 2). Thus, surgery treatment is still needed for the PAP-positive PCA patients, and it should be paid attention to that these individuals may present a poorer outcome than the negative ones. In this way, it strongly suggest that serum PAP should be reused in the clinic work for the detection of the disease progress and the prognosis.

5. Limitations

No serum PSA level is available as the NCI removed PSA data from SEER after the "substantial number of registry-reported PSA values were incorrect" [22]. In this research, no exact PAP level was present as the method used for detection is varied and in SEER only qualitative results were present in this database. As is reported by Andras G. Foti et al. in 1977 [23], there are different methods and the relative reference value according to different methodologies. Thus, only PAP+ or PAP- were present in this study according to the SEER database. As the median age of all patients in the study is 68 (61-74), the proportion alive in the survival curve is approaching to zero after approximately 200 months. Thus, no significant differences are observed in the long-term survival analysis. Moreover, as the data were only available between 1998 and 2003 and the other data were substituted by PSA test for the PCAs early-stage screening, more researches may be needed in the future study, especially for some high quality prospective clinic study.

6. Conclusions

In conclusion, despite of these limitations, our study provides insight into the PAP prediction in PCAs patients in the United States. It lends support to the consideration of testing PAP for the PCAs progress and the prognosis. Is this indicating the renewal of PAP?

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of Interest

None of the authors declare competing financial interests.

Authors’ Contributions

Huan Xu, Fubo Wang, and Huizhen Li contributed equally to this work.

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