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ORIGINAL ARTICLE

# Incorporating non-biological factors into the TNM staging system for better prognostication and decision-making in testicular cancer

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## Abstract

**Background** We combined county-level socioeconomic status (SES), marital status and insurance status to introduce NBF-stage, which were further incorporated into the American Joint Committee on Cancer (AJCC) TNM staging system to generate an integrated staging system for better prognostication and decision-making for testicular cancer patients.

**Methods** 15,324 eligible patients diagnosed with primary testicular cancer between January 1, 2007 and December 31, 2015 were strictly selected from the Surveillance, Epidemiology, and End Results (SEER) database. Independent survival predictors were determined based on Cox proportional hazards model. The Kaplan–Meier survival curves were conducted to describe the difference in predicting survival probability and the Multivariate Cox proportion hazard regression analyses were established to compare the cancer-specific survival (CSS) and overall survival (OS) difference among NBF stages or NBF–TNM subgroups.

**Results** County-level SES, marital status and insurance status were independent prognostic non-biological factors (NBFs) in our study ($P < 0.05$). NBF-stage (combination of SES, marital status, and insurance status) was also an independent survival predictor in TC ($P < 0.05$). NBF1 patients had 167% increased risk of cancer-specific mortality (CSM) as compared to NBF0 patients in testicular cancer ($P < 0.01$). And NBF0 patients all had a better CSS as compared to NBF1 patients of the same TNM stage both in seminoma and non-seminomatous germ cell tumor ($P < 0.05$).

**Conclusions** Incorporation of NBFs into AJCC TNM staging system in testicular cancer would potentially impact treatment decisions where treatments would not be rendered for a typically curable cancer with multi-modal therapy.

**Keywords** Non-biological factors · AJCC TNM stage · SEER · Testicular cancer, stage I

## Abbreviations

| | |
|---|---|
| NBF | Non-biological factor |
| TC | Testicular cancer |
| TGCT | Testicular germ cell tumor |
| AJCC | American Joint Committee on Cancer |
| IGCCCG | International Germ Cell Cancer Collaborative Group |
| TNM | Tumor, Node, Metastasis |
| SES | Socioeconomic status |
| SEER | Surveillance, Epidemiology, and End Results |
| CSS | Cancer-specific survival |
| CSM | Cancer-specific mortality |
| hCG | Human chorionic gonadotrophin |
| AFP | Alpha-fetoprotein |
| SGCT | Seminomatous germ cell tumor |
| NSGCT | Non-seminomatous germ cell tumor |
| CI | Confidence interval |
| SGCT | Seminomatous germ cell tumor |
| NSGCT | Non-seminomatous germ cell tumors |

Yongqiang Huang and Haoyue Sheng contributed equally to this work.

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## Introduction

Testicular cancer (TC) represents 0.5% of all newly diagnosed neoplasms, with 5.7 new cases and 0.2 death occurring per 100,000 men/per year during 2011–2015 in the United States [1]. And at diagnosis, the predominant histology of TC is testicular germ cell tumors (TGCT, 90–95% of cases) [2]. Testicular cancers show excellent cure rates [3] and the prognosis of which can be assessed against the biological factors and non-biological factors (NBFs). And several studies have sustained the prognostic importance of biological factors in TC, such as American Joint Committee on Cancer (AJCC) staging system [4, 5], histology of primary tumor [6] and tumor size [7]. And the effect of NBFs, for instance, health insurance [8, 9], marital status [7, 10], and county-level socioeconomic status (SES) [10] on the survival of the patients with testicular tumors have also been wildly studied. However, there are no available studies investigating the prognostic significance of NBFs together in TC. Of note, more than 95% TC patients with stage I disease were cured regardless of choice of clinical management [11]. Therefore, avoiding overtreatment for individuals with stage I testicular cancer have become one of the concerns of urologists. Furthermore, for metastatic testis tumors, the staging system of International Germ Cell Cancer Collaborative Group (IGCCCG) defined a prognostic factor-based staging system by incorporating TNM classification, histology, location of primary tumor and location of metastases to improve the accuracy of prognostication [12], which suggested that the prognostic prediction of AJCC TNM staging system was not perfect for advanced TC. Recently, several studies even showed the need of an improved risk stratification beyond the IGCCCG for TC [13, 14]. Therefore, with the aim of improving the prognostication of TNM staging system for TC and providing a better clinical management for individuals with testis tumors, we investigated NBFs (including marital status, insurance status, and SES) together. The major hypothesis of current study was that adding NBFs into TNM staging system could improve the accuracy of predicting the testicular cancer-specific survival (CSS) and which may assist urologists in the treatment and/or decision-making process. Our analysis relied on a large, contemporary (2007–2015), population-based cohort of individuals with TGCT ($n = 15{,}324$).

## Methods

### Study design and data source

The study cohort derived from the Surveillance, Epidemiology, and End Results (SEER) database, which encompasses approximately 28% of the American population. Using the SEER-stat software (SEER* 8.3.4), we selected the target population: 20,317 patients diagnosed with primary testicular cancer between January 1, 2007 and December 31, 2015 from the SEER database. We then identified testicular cancer cases with known NBFs: marital status, insurance status, year of diagnosis and county-level SES (including county-level median family income, county percent of adults in poverty, county percent unemployment and county percent of individuals without a high school education). We then discarded patients aged < 18 years (usually unmarried) and aged ≥ 65 years (usually eligible for Medicare benefits). And further exclusions including unknown race, unknown AJCC TNM stage, unknown if surgery performed, unspecific surgery performed, non-germ cell tumor histology and unknown cancer-specific death. Our final target cohort: accessible TGCT patients with known NBFs and known AJCC TNM stage ($n = 15{,}324$) (Fig. 1).

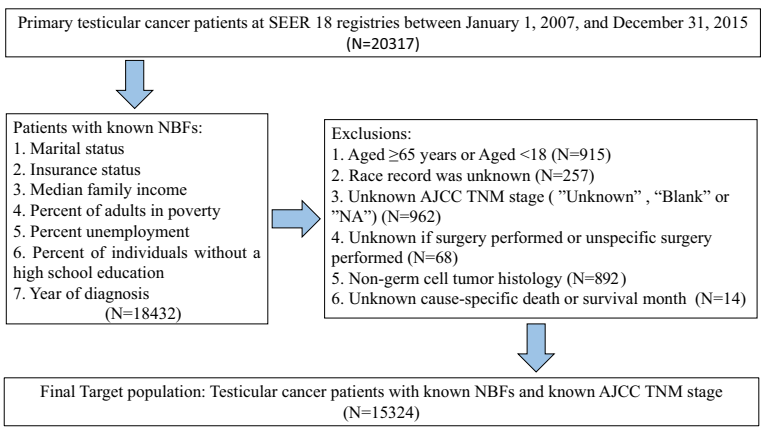


**Fig. 1** Flow diagram of target patients selected from SEER database

## Description of variables

Race was classified into white, black, and other, and year of diagnosis was separated into 2007–2011 and 2012–2015 in our final analysis. Primary tumor location consisted of right, left and "bilateral or other". According to International Classification of Diseases for oncology, 3rd Edition (ICD-O-3), seminoma (9061–9063) was distinguished from non-seminoma (9070, 9071, 9080–9085, 9100, 9012–9013). AJCC TNM stage was categorized as stage I, stage II, and stage III. Age was divided into three subtypes (≤ 29 years vs. 30–39 years vs. ≥ 40 years) and procedure of surgery was described as orchiectomy, orchiectomy with retroperitoneal pelvic lymph node dissection (RPLND) or surgery not performed [15]. Insurance status was defined as insured, Medicaid, uninsured and marital status including married, single, divorced/separated and widowed. Community-level variables were recorded at an interval of 4 or 5 years (2007–2011, 2012–2015) in the SEER database. Average value of Community-level variables between 2007–2011 and 2012–2015 was used to measure county-level SES. Four dimensions of a community's socioeconomic conditions, including median family income, percent of adults in poverty, percent unemployment and percent of individuals without a high school education were used to create a composite index of community SES, as described previously [15–17]. Subsequently, SES was divided into three groups (upper third, middle third, and lower third) based on the tertiles of the composite score.

## Identification of NBFs with independent prognostic significance and the corresponding statistical analyses

We used Cox proportional hazards models to identify the independent prognostic variables at a median survival time of 44 (rang from 0 to 107) months in current analyses. We selected all the prognostic factors associated with $P$ value < 0.2 in the univariate analysis containing the NBFs (marital status, insurance status, county-level SES and year of diagnosis). And among these four NBFs, using multivariate Cox proportional hazard regression analysis, we finally found that marital status, insurance status, and county-level SES could independently predict the CSS in TGCT (controlling for TNM stage, age at diagnosis, race, surgery and primary tumor location) and the corresponding hazard ratios were shown with 95% confidence intervals (CIS) in Table 2.

## Definition of NBF-score and NBF-stage (a new risk stratification)

We created a new risk stratification tool (we named it NBF-stage) by combination of three NBFs (including marital status, insurance status, and county-level SES). First, as shown in Fig. 2a, the subgroups of these three NBFs were listed with the corresponding hazard ratios which were further treated as the prognostic points. Second, we incorporated these three NBFs by calculating the sum of the points of the three NBFs and the sum was renamed NBF-score. For instance, NBF-score of a married and insured man who belonged to middle third SES was equal to the "1.275", "1", and "1.151", which was equal to 3.426. Then, NBF-score for all the target patients in our study cohort was calculated, which ranged from 3–7.376. The NBF-score of "7.376'' had the highest testicular cancer-specific mortality (CSM) while "3" had the lowest. And the Fig. 2b showed the association among the subgroups of these three NBFs. Finally, using NBF-score "3.956" (the median value of NBF-score of the whole study cohort) as cutoff, we assigned lower NBF-score (3-3.956) to NBF-stage 0 (NBF0) and classified higher NBF-score (3.426-7.376) into NBF-stage 1 (NBF1).

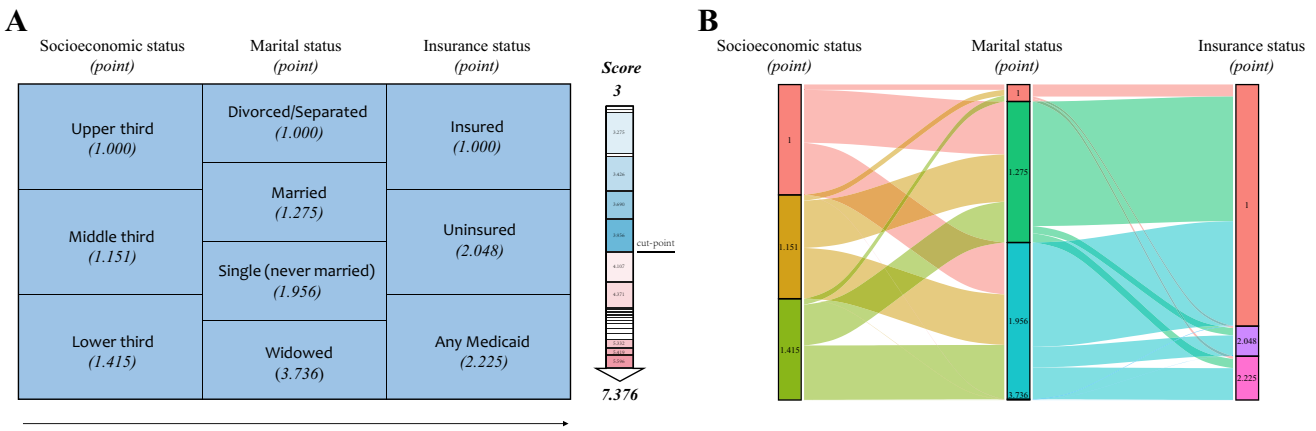


**Fig. 2** **a** NBF-score in testicular cancer: risk-stratifications. **b** Graphical summary of the distribution and association of different subgroups in county-level social status, marital status and insurance status, respectively

### Statistical analyses of survival

Multivariate Cox proportion hazard regression analysis was established to evaluate the survival probability of NBF-stage alone or NBF–TNM substages (NBF-stage combined with TNM staging system). The Kaplan–Meier survival curves were conducted to describe the difference in predicting survival probability and the log-rank tests to determine the statistical significance. CSS was used as the endpoint to generate NBF-stage, and statistical significance was set at $P < 0.05$. All statistical analyses were performed based on statistic Package for social science (SPSS version 22; SPSS Inc., IL, USA).

## Results

A population-based competing risk analysis of 15,324 TGCT patients from the SEER registries was conducted in current study. After a follow-up duration between 0 and 107 (median was 44) months, 437 (2.85%) TGCT-related death occurred. Baseline characteristics are summarized in Table 1.

### Three NBFs were significant and independent predictors for the CSS of TGCT

Univariate analysis of potential survival predictors identified biological factors (race, tumor location, histology, TNM stage, surgery, age at diagnosis) and NBFs (year of diagnosis, SES, insurance status, marital status) ($P < 0.02$, data no shown). Subsequently, multivariate Cox hazard regression analysis of all these factors found that all biological factors were independently associated with CSS in TGCT patients while NBFs including SES, marital status, and insurance were significant predictors for CSS in TGCT (Table 2).

### TGCT patients' distribution were uneven among NBF-score subgroups or among three NBFs

As shown of the arrow in Fig. 2a, NBF-score ranged from 3 to 7.376 in the whole study cohort. The blue area represented lower NBF-score subgroup (NBF0) while the red represented higher NBF-score subgroup (NBF1). The proportion of patients in each NBF-score subgroup could be measured according to the area it covered in the arrow. Obviously, the majority of TGCT patients belonged to NBF-score "3.275" (15.5%), "3.426" (13.4%), "3.69" (10.6%), "3.956" (12.6%) or "4.107" (10.9%) subgroup. And Fig. 2b may partly explain the uneven proportion among NBF-score subgroups: 1: In marital status, married [points = 1.275 (44.7%)] or single [point = 1.956 (49.6%)] account for the majority. 2: For insurance status, the majority of TGCT patients were insured [point = "1" (76.5%)]. 3: Compared to married patients, single patients were more likely to reside in lower third SES counties (point = "1.415", 28.9% vs. 34.7% respectively). 4: And 88.3% of married patients were insured while only 66.6% of unmarried patients were insured.

**Table 1** Baseline characteristics of testicular cancer patients included in our study

| Characteristic | No. (%) |
|---|---|
| Race | |
| White | 14,031 (91.6) |
| Black | 461 (3.0) |
| Other | 832 (5.4) |
| Year of diagnosis | |
| 2007–2011 | 8140 (53.1) |
| 2012–2015 | 7184 (46.9) |
| Tumor location | |
| Right testis | 7941 (51.8) |
| Left testis | 7211 (47.1) |
| Bilateral testis or other | 172 (1.1) |
| Histology | |
| Seminoma | 8798 (57.4%) |
| Non-seminoma | 6526 (42.6%) |
| AJCC stage | |
| Stage I | 11,291 (73.7) |
| Stage II | 1979 (12.9) |
| Stage III | 2054 (13.4) |
| Surgery | |
| Orchiectomy | 13,541 (88.4) |
| Orchiectomy and RPLND | 1506 (9.8) |
| Surgery not performed | 277 (1.8) |
| Age group, years | |
| ≤ 29 | 5872 (38.3) |
| 30–39 | 5019 (32.8) |
| ≥ 40 | 4433 (28.9) |
| Socioeconomic status | |
| Upper third | 5360 (35.0) |
| Middle third | 5044 (32.9) |
| Lower third | 4920 (32.1) |
| Insurance status | |
| Insured | 1172.7 (76.5) |
| Medicaid | 2137 (13.9) |
| Uninsured | 1460 (9.5) |
| Marital status | |
| Married | 6847 (44.7) |
| Single | 7608 (49.6) |
| Divorced/separated | 827 (5.4) |
| Widowed | 42 (0.3) |

**Table 2** Multivariate Cox regression analyses of CSS

| Variable | Reference | Characteristic | Cancer-specific survival | | |
|---|---|---|---|---|---|
| | | | HR (95%) | SE | *P* value |
| Race | White | Black | 1.34 (0.89–2.03) | 0.21 | 0.16 |
| | | Other | 1.52 (1.06–2.19) | 0.19 | 0.02 |
| Year of diagnosis | 2007–2011 | 2012–2015 | 1.07 (0.87–1.30) | 0.55 | 0.10 |
| Tumor location | Right testis | Left testis | 0.92 (0.75–1.12) | 0.10 | 0.41 |
| | | Bilateral testis or other | 1.34 (0.87–2.06) | 0.22 | 0.19 |
| Histology | Seminoma | Non-seminoma | 2.83 (2.22–3.61) | 0.12 | < 0.01 |
| AJCC stage | Stage I | Stage II | 2.53 (1.68–3.80) | 0.21 | < 0.01 |
| | | Stage III | 14.86 (11.26–19.61) | 0.14 | < 0.01 |
| Surgery | Orchiectomy | Orchiectomy and | | | |
| | | RPLND | 0.59 (0.42–0.82) | 0.17 | < 0.01 |
| | | Not performed | 3.01 (2.15–4.21) | 0.17 | < 0.01 |
| Age group, years | ≤ 29 | 30–39 | 1.44 (1.13–1.83) | 0.12 | < 0.01 |
| | | ≥ 40 | 2.53 (1.96–3.28) | 0.13 | < 0.01 |
| Socioeconomic status | Upper third | Middle third | 1.15 (0.87–1.50) | 0.13 | 0.29 |
| | | Lower third | 1.42 (1.10-1.82) | 0.13 | < 0.01 |
| Insurance status | Insured | Medicaid | 2.23 (1.78–2.79) | 0.14 | < 0.01 |
| | | Uninsured | 2.05 (1.56–2.70) | 0.11 | < 0.01 |
| Marital status | Divorced/ | | | | |
| | Separated | Married | 1.28 (0.82–1.97) | 0.22 | 0.28 |
| | | Single | 1.96 (1.29–2.98) | 0.21 | < 0.01 |
| | | Widowed | 3.74 (1.30–10.76) | 0.54 | 0.15 |

**Table 3** Multivariable Cox regression analyses of independent prognostic factors in testicular cancer

| Variable | Reference | Characteristic | Cancer-specific survival | | |
|---|---|---|---|---|---|
| | | | HR (95%) | SE | *P* value |
| Race | White | Black | 1.32 (0.88–1.99) | 0.21 | 0.19 |
| | | Other | 1.50 (1.05–2.16) | 0.19 | 0.03 |
| Year of diagnosis | 2007–2011 | 2012–2015 | 1.08 (0.89–1.33) | 0.43 | 0.10 |
| Tumor location | Right testis | Left testis | 0.93 (0.76–1.14) | 0.10 | 0.47 |
| | | Bilateral testis or other | 1.38 (0.90–2.12) | 0.22 | 0.14 |
| Histology | Seminoma | Non-seminoma | 2.78 (2.19–3.54) | 0.12 | < 0.01 |
| AJCC stage | I | II | 2.61 (1.74–3.92) | 0.21 | < 0.01 |
| | | III | 15.78 (11.98–20.79) | 0.14 | < 0.01 |
| Surgery | Orchiectomy | Orchiectomy and | | | |
| | | RPLND | 0.56 (0.40–0.78) | 0.17 | < 0.01 |
| | | Not performed | 2.89 (2.08–4.04) | 0.17 | < 0.01 |
| Age group, y | ≤ 29 | 30–39 | 1.41 (1.11–1.78) | 0.13 | < 0.01 |
| | | ≥ 40 | 2.37 (1.86–3.03) | 0.13 | < 0.01 |
| NBF-stage | NBF0 | NBF1 | 2.67 (2.13–3.35) | 0.12 | < 0.01 |

## NBF-stage was an independent predictor of survival outcome in TGCT

NBF-stage 0 (NBF0) (NBF-score = 0–3.956) included 8572 patients (55.9%) while NBF-stage I (NBF1) (NBF-score = 4.107–7.376) covered 6752 patients (44.1%). Table 3 showed NBF1 was strongly associated with lower CSS with 167% increased risk of cancer-specific mortality [Hazard ratio (HR) = 2.67, 95% CI 2.13–3.15, $P < 0.01$] in our current analysis. Kaplan–Meier plots and life table revealed that the overall 5-year CSS of NBF0 and NBF1 was 98.37% and 93.74%, respectively ($P < 0.01$, Fig. 3a) and overall 5-year OS of NBF0 and NBF1 was 97.13% and 91.61%, respectively ($P < 0.01$, Fig. 3b).

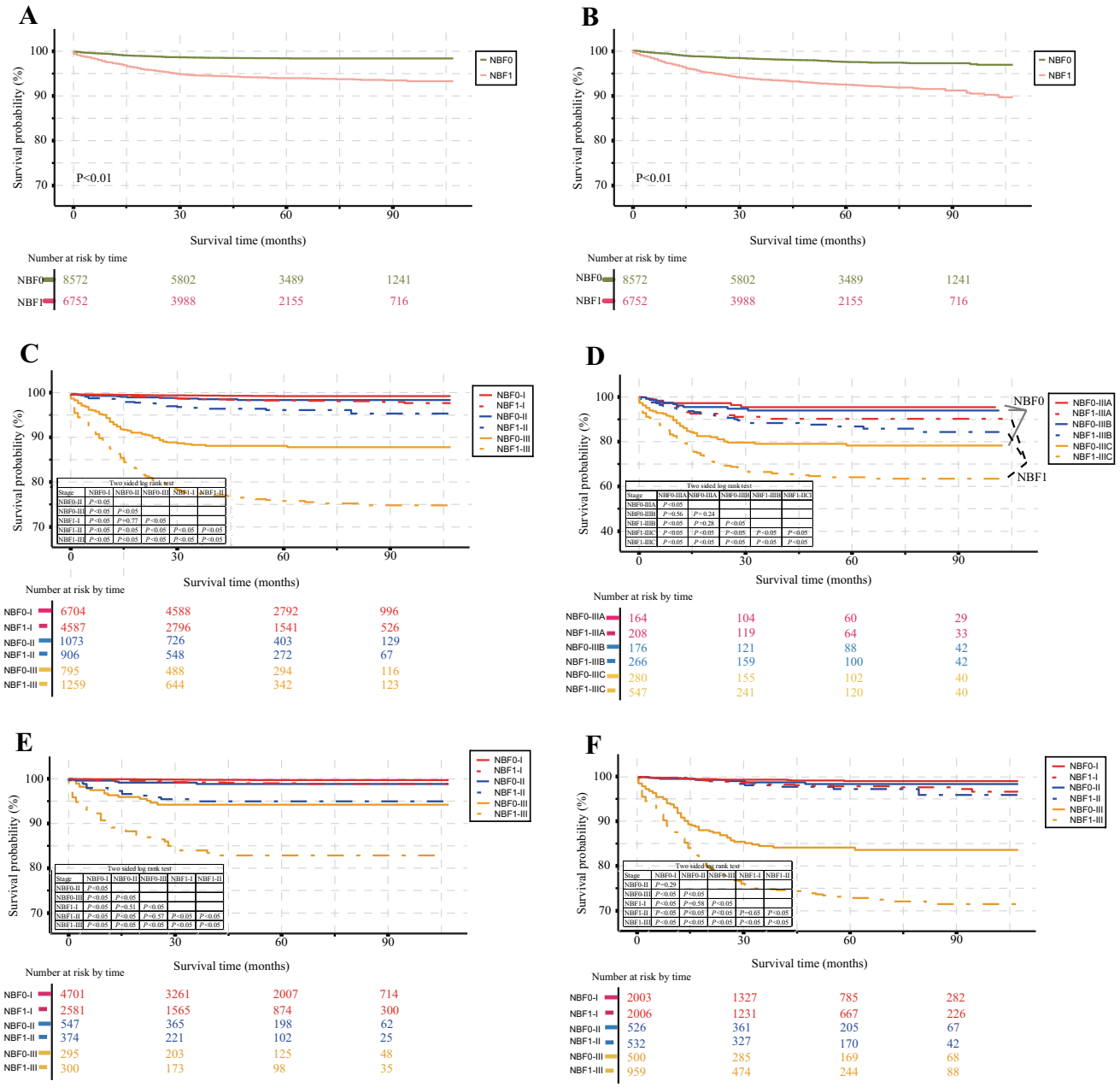


**Fig. 3** Kaplan–Meier survival curves of NBF-staging and NBF–TNM staging system. **a** CSS of NBF0 and NBF1. **b** OS of NBF0 and NBF1. **c** CSS of NBF0-I, NBF1-I, NBF0-II, NBF1-II, NBF0-III and NBF1-III in testicular cancer patients. **d** CSS of NBF0-IIIA, NBF1-IIIA, NBF0-IIIB, NBF1-IIIB, NBF0-IIIC and NBF1- IIIC in testicular cancer patients. **e** CSS of NBF0-I, NBF1-I, NBF0-II, NBF1-II, NBF0-III and NBF1-III in seminomatous germ cell tumor (SGCT). **f** CSS of NBF0-I, NBF1-I, NBF0-II, NBF1-II, NBF0-III and NBF1-III in non-seminomatous germ cell tumors (NSGCT)

## Prognostic significance of AJCC TNM stage (I, II or III) combined with NBF-stage (NBF0 or NBF1)

Kaplan–Meier survival curves and life tables were used to analyze the prognostic significance of the NBF–TNM substages which was the combination of TNM stage and NBF-stage. NBF–TNM substage (NBF0 and NBF1) was incorporated into TNM stage (stage I, II and III) in the overall cohort ($n = 15{,}324$). Compared to NBF0, NBF1 was statistically associated with decreased CSS ($P < 0.05$) in all the, respectively, TNM stages (stages I, II and III). Of note, NBF-stage well subdivided TNM stage III into NBF0-stage III (NBF0-III) and NBF1-stage III (NBF1-III) (5-year CSS 85.89% vs. 71.90%) ($P < 0.05$) (Fig. 3c). Nevertheless, no statistically significant benefit in CSS between NBF1-stage I (NBF1-I) and NBF0-stage II (NBF0-II) at 107 months' of follow-up was

**Table 4** Prognosis of NBF–TNM stage in testicular cancer

| Stage | No. of patients | Cancer-specific survival | | |
|---|---|---|---|---|
| | | HR (95% CI) | SE | *P* value |
| NBF0-I | 6704 | 1.000 (Reference) | – | – |
| NBF1-I | 4587 | 3.722 (2.237–6.193) | 0.26 | < 0.01 |
| NBF0-II | 1073 | 2.888 (1.395–5.978) | 0.37 | < 0.01 |
| NBF1-II | 906 | 9.157 (5.121–16.374) | 0.30 | < 0.01 |
| NBF0-III | 795 | 21.422 (13.212–34.734) | 0.25 | < 0.01 |
| NBF1-III | 1259 | 51.039 (32.510–80.128) | 0.23 | < 0.01 |

observed in Fig. 3c ($P = 0.77$). The multivariate Cox regression analyses revealed the HRs among each NBF–TNM substages, the prognostic prediction of which was consistent with the Kaplan–Meier analysis. Table 4 showed that NBF1 patients had higher HRs compared to the corresponding NBF0 patients and NBF0-stage II (NBF0-II) had lower HRs compared to TNM NBF1-I. Of note, the proportion of NBF1 increased in patients with TNM stages I to III (40.63% in TNM stage I vs. 45.78% in II vs. 61.30% in III, $P < 0.05$).

### Prognostic prediction of AJCC TNM substages incorporated with NBF-stage (NBF0 or NBF1)

Subsequent analysis excluded non-specific TNM stage including (I NOS, II NOS and III NOS, $n = 5269$, 744 and 413, respectively) and used Kaplan–Meier survival curves and life tables. Adding NBF-stage into TNM stage I or stage II showed non-significant CSS rates among the NBF–TNM substages except-NBF0-IS and NBF1-IS (5-year CSS of 98.82% vs 96.78, respectively, $P < 0.05$). Univariate Kaplan–Meier CSS analysis showed that TNM stage II C had inferior CSS to II B or IIA ($P < 0.05$), but the CSS difference disappeared when incorporated NBF-stage into TNM stage. Herein, NBF-stage could further divided TNM stage III into six prognostically different groups (Fig. 3d). All NBF1 patients showed a significant decreased CSS as compared to the NBF0 patients ($P < 0.05$) in all the respective AJCC TNM stage III substages. In addition, there was no apparently different CSS between NBF0-IIIB and IIIA (NBF0 or NBF1, $P = 0.56$ and $P = 0.24$, respectively). The multivariate Cox regression analyses showed the HRs of all the NBF–TNM substages in supplementary Table 1. Of note, as both subgroup of TNM stage III, NBF1-IIIC showed a significantly decreased CSS as compared to NBF0-IIIA (HR = 238.118 and 25.577, respectively, $P < 0.05$).

## Discussion

Testicular cancer (TC) has the highest prevalence in the Europe, Australia and America, and the lowest incidence rates are found in Asia and Africa [18]. In the United States, TC is most frequently diagnosed among men aged 20–34 (account for more than 50% new cases) [1]. Based on their chemosensitivity, adequate early treatment, strict follow-up and salvage therapies, the vast majority of testicular cancers will be cured, and 5-year relative survival rates are approximately 95% in the U.S. and Europe [1, 19].

However, concerning the prognostic value of NBFs in TC, only a limited number of studies were available. A population-based study from USA SEER database analyzed patients who diagnosed with TC between 1973 and 2005 and concluded that married men were more likely to be stage I and had improved testis CSS as compared to unmarried men [20]. Similar results have been reported in another study in 27,948 patients with TC [10]. And higher cancer-specific morbidity (CSM) has been observed in patients without insurance and patients with Medicaid in comparison with those who are insured in two retrospective studies [8, 9]. In TC, as compared to intermediate and high SES categories, patients in the lowest SES level had significantly higher CSM [10]. Currently, the results of our study also confirmed the prognostic significance of these NBFs in TC, including marital status, insurance status, and county-level SES.

Many theories were postulated to explain the survival difference among testicular cancer patients of different marital status, insurance status, or county-level SES. In TC, compared to married men, unmarried men were more likely to be advanced diseases [20] and were at risk for decreased treatment adherence [20, 21]. In TC, compared to insured men, men without insurance and men with Medicaid insurance were more likely to present with a later stage of disease or larger tumor size at diagnosis and received fewer treatments [8, 9]. And the reduced likelihood of receiving radiotherapy was observed in TC patients who lived in a low SES county [22]. In present study, as shown in Supplemental Table 2, compared to NBF0 patients, NBF1 patients were more likely to have stage III disease (9.3% vs. 18.6%, respectively, $P < 0.05$), and more likely to be younger (25.4% ≤ 29 years vs. 54.7% ≤ 29 years, $P < 0.05$). Of note, all of NBF0 patients were insured while only 46.7% NBF1 patients were insured ($P < 0.05$). And 70.6% NBF0 patients were married while 84.0% NBF1 patients were unmarried ($P < 0.05$).

For testicular cancer, the 2017 Tumor, Node, Metastasis (TNM) of the International Union Against Cancer (UICC) have been widely used as the recommended staging system. It should be noted that this TNM staging system includes assessment of serum tumor markers, including nadir values of hCG, AFP and LDH after orchiectomy (S category). To predict survival outcomes of metastatic germ cell cancer, the staging system of IGCCCG combined the TNM staging system with histology, location of the primary tumor, location of metastases and pre-chemotherapy marker levels in serum and finally categorized patients into 'good', 'intermediate' or 'poor' prognosis [12]. A retrospective study from 2015

shows that age-integrated IGCCCG is more discriminatory [14], which indicates that the TNM staging is not yet optimal for the prediction of prognosis of TC patients. Therefore, other prognostic factors should be incorporated into the present TNM classification [13]. However, according to our knowledge, the prognostic value of NBFs has not been well investigated and the current study aim to improve prognostication of testicular cancer using an integrated staging system which combined NBFs with TNM substages.

First, we demonstrated that NBF-stage (based on county-level SES, marital status and insurance status) was an independent prognostic factor in TC patients. Then we classified testicular patients into two subgroups (NBF0 and NBF1) and found that NBF1 had a higher risk of cancer-specific mortality as compared to NBF0 [(HR) = 2.67, $P < 0.01$]. We further incorporated NBF-stage into TNM staging system (stages I, II, and III) to generate integrated staging system (NBF0-I, NBF1-I, NBF0-II, NBF1-II, NBF0-III and NBF1-III) and we also found that NBF1 had a worse CSS as compared to NBF0 of the same TNM stage. Of note, NBF1-I had no statistically CSS benefit as compared to NBF0-II ($P = 0.77$). Finally, using NBF-stage, we subdivided TNM stage III into six groups (namely NBF0-IIIA, NBF1-IIIA, NBF0-IIIB, NBF1-IIIB, NBF0-IIIC and NBF1-IIIC). Further analysis also revealed that NBF1 had a worse prognosis than NBF0 of the same TNM stage III substages. Interestingly, there were no CSS differences between NBF1-IIIA and III B (NBF0-IIIB or NBF1-IIIB, $P = 0.24$, $P = 0.28$, respectively). And NBF0-IIIB showed no worsening CSS compared to III A (NBF0-IIIA, NBF1-IIIA, $P = 0.56$, $P = 0.24$, respectively).

Furthermore, we investigated NBFs in seminomatous germ cell tumor (SGCT) and non-seminomatous germ cell tumors (NSGCT) separately, due to the different prognosis and clinical management of these two subtypes. Similarly, better CSS outcomes were seen in NBF0 patients of each TNM stage in both SGCT and NSGCT. However, in seminoma there was no CSS difference between NBF1-II and NBF0-III ($P = 0.57$) or NBFI-I and NBF0-II ($P = 0.51$). And in NSGCT, NBF1-I patients showed no better CSS compared to TNM stage II (NBF0-II or NBF1-II, $P = 0.58$, $P = 65$, respectively).

For the treatment of TNM stage I SGCT, several available studies recommended to adopt risk-adapted treatment [23, 24]. Using tumor size > 4 cm and stromal rete testis invasion as risk factors, these studies finally subdivided SGCT patients into low- and high-risk groups for occult metastatic disease. And a prospective trial confirmed the feasibility of this risk-adapted treatment: SGCT patients with both risk factors were recommended adjuvant carboplatin while patients with 0 to one risk factors were managed with active surveillance [25]. Similarly, for the treatment of TNM stage I NSGCT, based on the risk factor of vascular invasion, risk-adapted policy was also recommended by several studies [26, 27]. And NSGCT patients with vascular invasion were recommended to undergo adjuvant chemotherapy and patients without vascular invasion were recommended a surveillance strategy. In the present study, patients of TGCT NBF1-I had a relatively low CSS as compared to patients of TGCT NBF0-I (HR = 3.722, 95% CI 2.237–6.193, $P < 0.01$) (Table 4). The result also could be confirmed in both stage I SGCT and stage I NSGCT.

Therefore, for stage I disease, we provided following suggestions: 1: NBF-stage might be added to the risk-adapted policy which might improve the effectiveness of risk-adapted management and select patients with perfect outcomes so as to avoid overtreatment. 2: The minimal follow-up should be tailored to NBFI and NBF0. For instance, patients of NBF1-I should be informed that they might have higher risk of dying from TC as compared to NBF0-I, which may increase their treatment adherence. And we advised that more doctor visits should be recommended to NBF1 patients. (As EAU guideline recommended 2 times and 4–6 times for SGCT and NSGCT in the first year, respectively). And further studies will be needed to determine whether additional computed tomography/magnetic resonance imaging should be provided for NBF1 patients.

For the treatment of advanced TC diseases, the prognostic-based staging system for metastatic germ cell cancer of IGCCCG was widely used. The current study found NBF-stage could significantly subdivide stage III and II patients into subgroups with statistically different survival (as shown in Fig. 3e–f and Supplemental Table 1). The incorporation of NBF-stage into TNM stage II and III could improve prognostication in advanced TC, which suggested that NBF-stage-integrated IGCCCG might be more discriminatory. The NBF1-III TC patients were at a highest risk of CSM compared to NBF0-I (HR = 238.12, 95% CI 58.59–967.76, $P < 0.05$) (Supplemental Table 1). Therefore, we recommended that these patients should be transferred to a high volume center with a better reported outcomes for TC patients with advanced diseases [18].

Our study included a large population of testicular cancer patients, but was also subjected to several limitations. First, it might not be accuracy to classify TC individuals based on county-level SES, which needs to be further investigated. Second, our study did not include patients aged more than 65 years, due to the insurance status. The number of cycles of chemotherapy administered was not recorded in SEER database which might partly influence the results presented in current study. Since coding of death items was done independently by expert oncologists, the influence of any misclassification could be neglected [10]. And our analyses were the retrospective study design. Therefore, prospective, controlled, non-randomized trials were essential to be performed.

## Conclusions

We used county-level socioeconomic status (SES), marital status and insurance status as prognostic factors to introduce NBF-stage which divided testicular cancer patients into two groups (NBF0 and NBF1) with statistically different CSS and OS. We then proposed an integrated staging system (NBF–TNM staging system) which incorporated NBF-stage into AJCC TNM staging system. We found that –NBF0 patients all had a better CSS than NBF1 patients of the same TNM stage both in seminoma and non-seminomatous germ cell tumor, which improved the precision of prognostic prediction in TC. Therefore, in TC, incorporation of NBF-stage into present AJCC TNM staging system would potentially impact treatment decisions where treatments would not be rendered for a typically curable cancer with multi-modal therapy.

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### Compliance with ethical standards

**Conflict of interest** This paper does not contain any studies with human participants or animals. Informed consent was not needed because the present study based on a publicly available database without identifying patient information. The author has no relevant affiliations or financial conflict with the subject matter or materials discussed in the manuscript. Peer reviewers on this article have no special financial or relationships to declare.

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