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ORIGINAL RESEARCH

Predictors of inguinal lymph node metastasis in penile cancer patients: a meta-analysis of retrospective studies

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Jiao Hu[1]
Yu Cui[1]
Peihua Liu[1]
Xu Zhou[2]
Wenbiao Ren[1]
Jinbo Chen[1]
Xiongbing Zu[1]

[1]Department of Urology, Xiangya Hospital, Central South University, Changsha, People's Republic of China; [2]Reproductive Medicine Center, Xiangya Hospital, Central South University, Changsha, People's Republic of China

Purpose: Inguinal lymph node metastasis (LNM) is one of the most significant prognostic factors for patients with penile cancer. This study aimed to identify potential predictors of inguinal LNM.

Patients and methods: A comprehensive search of the PubMed, Embase, and Cochrane Library databases for studies that reported predictors of inguinal LNM in penile cancer was performed. Finally, we selected 42 eligible studies with 4,802 patients. Accumulative analyses of odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were performed. All analyses were performed by using Review Manager software version 5.3.

Results: Among the 4,802 patients, 1,706 (36%) were diagnosed with inguinal LNM. Predictors of LNM included two categories: tumor-associated biomarkers and invasive clinicopathologic characteristics. Biomarker-specific predictors: the program death ligand 1 (PD-L1) overexpression (OR=2.55, p=0.002), higher neutrophil-to-lymphocyte ratio (NLR) (OR=4.22, p=0.010), higher C-reactive protein (CRP) (OR=4.78, p<0.001), squamous cell carcinoma antigen (SCC-Ag) overexpression (OR=8.52, p<0.001), P53 protein overexpression (OR=3.57, p<0.001). Clinicopathological predictors: positive clinical lymph node (cN+) (OR=5.86, p<0.001), high-risk histopathological subtype (OR=14.63, p<0.001) and intermediate-risk subtype (OR=3.37, p<0.001), vertical growth pattern (OR=1.97, p=0.020), higher stage (AJCC: OR=3.66, p<0.001; UICC: OR=2.43, p<0.001), higher tumor grade (OR=3.37, p<0.001), tumor size (>3 cm) (OR=2.00, p=0.002), LVI (OR=3.37, p<0.001), invasion depth (>5 mm) (OR=2.58, p=0.002), nerve invasion (OR=2.84, p<0.001), corpora cavernosum invasion (OR=2.22, p<0.001), corpus spongiosum invasion (OR=1.73, p=0.002) and urethra invasion (OR=1.81, p=0.030).

Conclusion: Current meta-analysis conclusively identified valuable predictors of inguinal LNM for patients with penile cancer. However, high-quality studies are warranted to further validate our conclusions. The intrinsic link between these predictors needs to be further investigated to create an accurate mathematical prediction model for LNM.

Keywords: inguinal lymph node metastasis, penile cancer, predictor, meta-analysis

Correspondence: Xiongbing Zu; Jinbo Chen
Department of Urology, Xiangya Hospital, Central South University, Xiangya Road, Kaifu District, Hunan Province, Changsha 410008, People's Republic of China
Tel +86 7 318 975 3011
Fax +86 7 318 975 3280
Email whzuxb@163.com; chenjinbo1989@yahoo.com

Introduction

Penile cancer is a rare malignant tumor, which results in significant physiological and psychological effects on patients.[1] Inguinal lymph nodes are the first site of metastasis in penile carcinoma.[2] The presence of inguinal lymph node metastasis (LNM) is one of the most significant prognostic factors for patients with penile cancer.[3] Therefore, optimal management of inguinal lymph nodes is crucial for long-term survival after local treatment of the primary tumor.[4]

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The best management of clinically negative nodes (cN0) is controversial because of the approximately 25% likelihood of micrometastatic disease,[5,6] and complete detection of micro-metastases by current imaging techniques is difficult.[7] Close surveillance, dynamic sentinel node biopsy, and modified lymphadenectomy were recommended in the treatment of patients with cN0 over the past decades, aiming to decrease the complications caused by radical inguinal lymph node dissection (ILND).[4,8] But these methods remained a notable risk of missing micro-metastatic disease.[9,10] Comparing these methods, prophylactic lymphadenectomy has the best overall survival benefit from early resection of occult metastasis.[11,12] However, concurrent complications related to lymph drainage and wound healing are relatively high despite surgical modifications.[13–15] Therefore, accurate inguinal LNM prediction could pinpoint patients who are the best candidates for inguinal lymphadenectomy, which could not only achieve the best survival rate for patients with occult metastasis but also avoid unnecessary treatment for patients with a low risk of developing LNM.

Given the rarity of penile cancer, prior studies that attempted to identify predictors of LNM had several methodological limitations, such as small series, single-center, and lack of randomized controlled trials. Moreover, the results of these studies were discrepant. Several predictive models had been developed to stratify the risk of developing LNM, such as Solsona risk groups and Hungerhuber risk stratification.[16,17] Unfortunately, further validation denied the accuracy of these tools.[18] Furthermore, the prognostic value of several potential biomarkers, such as PD-L1, P53 protein, NLR, CRP, SCC-Ag, Ki-67, and HPV DNA, had not been conclusively established. Hence, we performed this comprehensive meta-analysis to determine the significant predictors of LNM in penile cancer.

Methods

This meta-analysis was conducted according to the preferred reporting items for systematic review and meta-analyses (PRISMA) statement and was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO ID: CRD42018107232).[19] It was approved by the institutional review board before initiation. The need for ethical standard approval or informed consent was waived due to the nature of the research design.

Search strategy

In accordance with the PRISMA guidelines, a literature search was performed in January 2019 using PubMed, Embase, and the Cochrane Library. Search terms used included the following: (((penile cancer) or (penile tumor) or (penile neoplasm) or (penile squamous cell carcinoma))) AND ((inguinal lymph node metastasis) or (lymph node metastases) or (nodal metastasis) or (inguinal node metastasis) or (inguinal lymphadenopathy) or (inguinal lymphadenectasis) or (inguinal lymph node involvement)) and ((predictors) or (predictive factor)). All studies on this topic were reviewed, and related references of original studies were identified by manual search.

Inclusion and exclusion criteria

The PICOS (Population, Intervention, Comparator, Outcome, and Study design) principle was employed to define study eligibility. Studies that compared penile cancer patients who were pathologically diagnosed with LNM (P) after local treatment of primary tumor (I) to patients without LNM (C) to determine clinicopathologic predictors or biomarkers of inguinal LNM (O) using logistic regression analyses or providing original statistical data (S) were considered relevant to this systematic review and meta-analysis. Eligible studies were selected based on the following: 1) precise definition of potential predictors; 2) sufficient data: odds ratios (ORs) with 95% confidence interval (CIs) or credible original statistical data that could be used to calculate ORs and 95% CIs; 3) pathologically confirmed LNM; 4) moderate or high methodological quality studies according to the Newcastle–Ottawa scale;[20] and 5) English studies with human subjects. Between two studies with similar research populations, study with larger sample size was chosen. All overlapping studies with different predictors were included. Relevant researches in the form of case reports, reviews, case series, editorials, or letters were excluded.

Data extraction

Data of identified studies were extracted by two independent reviewers (J.H. and J.B.C.). Discrepancies were resolved during a consensus meeting with a senior reviewer (X.Z.). The following information was extracted: author, year, country, sample size, LNM predictors, and follow-up period. We extracted the ORs with their 95% CIs directly if available in the article. Otherwise, we extracted the original statistical data to calculate the ORs and 95% CIs.

Quality of data assessment and risk of bias evaluation

Two independent reviewers evaluated the quality of the included studies using the Newcastle–Ottawa Quality Assessment Scale, which was designed to assess the quality of observational studies. A star system including nine scoring items was adapted to grade each study. A total score of 8 to 9 was defined as a high-quality study; 6 to 7, intermediate quality. Moreover, we evaluated the publication bias by visual inspection of funnel plots. We also performed a sensitivity analysis using the leave-one-out cross-validation to assess the stability of the present meta-analysis results.

Definition of predictors

Definitions of several predictors were recorded as previously published.[21] Clinically positive inguinal lymph nodes (cN+) were defined as those that are palpable or visible with imaging examinations. Histological grade was divided into three groups: G1 (well-differentiated), G2 (moderately differentiated), and G3 (poorly differentiated). There were two TNM systems, including the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC). Both of them had several versions. We defined T2 and greater stage as higher stage. Growth pattern was classified as superficial or vertical; Invasion depth was measured from the intact basement membrane at the edge of the primary tumor to the deepest infiltrating tumor cell. LVI was defined as the presence of cancer embolus in the lymphatic or vascular lumen that was detected by immunohistochemical staining. Histopathological subtypes were classified as low risk (verrucous, papillary, and warty), intermediate risk (usual SCCs and mixed forms), and high risk (basaloid, sarcomatoid, adenosquamous, and poorly differentiated types) according to the European Association of Urology (EAU) guidelines.[4] PD-L1, Ki-67, P53 protein, and HPV virus were measured in tumor. SCC-Ag, NLR, and CRP were measured in serum.

Statistical analysis

We performed this meta-analysis to identify potential predictors of LNM by pooling the predictor effect and its standard error, which was calculated from the available ORs and their 95% CIs or from original statistical data. The inverse variance method was adapted to evaluate the cumulative effects of these potential predictors. Statistical heterogeneity among the included studies was assessed using the Cochrane Q test and I^2 statistic (I^2<25%: no heterogeneity; I^2=25–50%: moderate heterogeneity; I^2>50%: large heterogeneity). The value of I^2 indicated the degree of heterogeneity. A random-effects model was used when there was a large heterogeneity; otherwise, the fixed-effects model was used. The level of statistical significance was set at 0.05. The meta-analyses were performed using Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results

Study population

Finally, we selected 42 eligible studies.[5,21–61] Among the included 4,802 patients, 1,706 (36%) were diagnosed with LNM. Figure 1 shows the study selection process. These studies were performed in the following geographical regions: Europe (n=12), South America (n=8), North America (n=10), Africa (n=1), Australia (n=1), and Asia (n=10). The characteristics of the included studies are provided in Table 1. The pooled results of the predictors are provided in Table 2. Original data are summarized in Tables S1–3. The symmetrical funnel plots showed in Figures S1 and S2 revealed low publication bias for these predictors.

Biomarker-specific predictors for LNM

Immune-related biomarkers: PD-L1, CRP, and NLR

Immune-related biomarkers as a predictor of LNM were reported in seven studies. For these predictors, heterogeneity was not observed. Cumulative analysis of these homogeneous data revealed that PD-L1 overexpression in tumor cells (OR 2.55, 95% CI 1.40–4.64; p=0.002), higher NLR in serum (OR 4.22, 95% CI 1.36–13.09; p=0.010) and higher level of CRP in serum (OR 4.78, 95% CI 2.48–9.20; p<0.001) are significant predictors of LNM (Figure 2A).

SCC-Ag and P53 protein

SCC-Ag overexpression as a predictor was reported in four studies. There was no heterogeneity between these studies (I^2=0%; p=0.88). Cumulative analysis of these data revealed that it (OR 8.52, 95% CI 4.09–17.78; p<0.001) is a significant predictor of LNM (Figure 2B). Similarly, there was no heterogeneity between four studies which reported the correlation between P53 and LNM (I^2=0%; p=0.68). Cumulative analysis of these homogeneous data

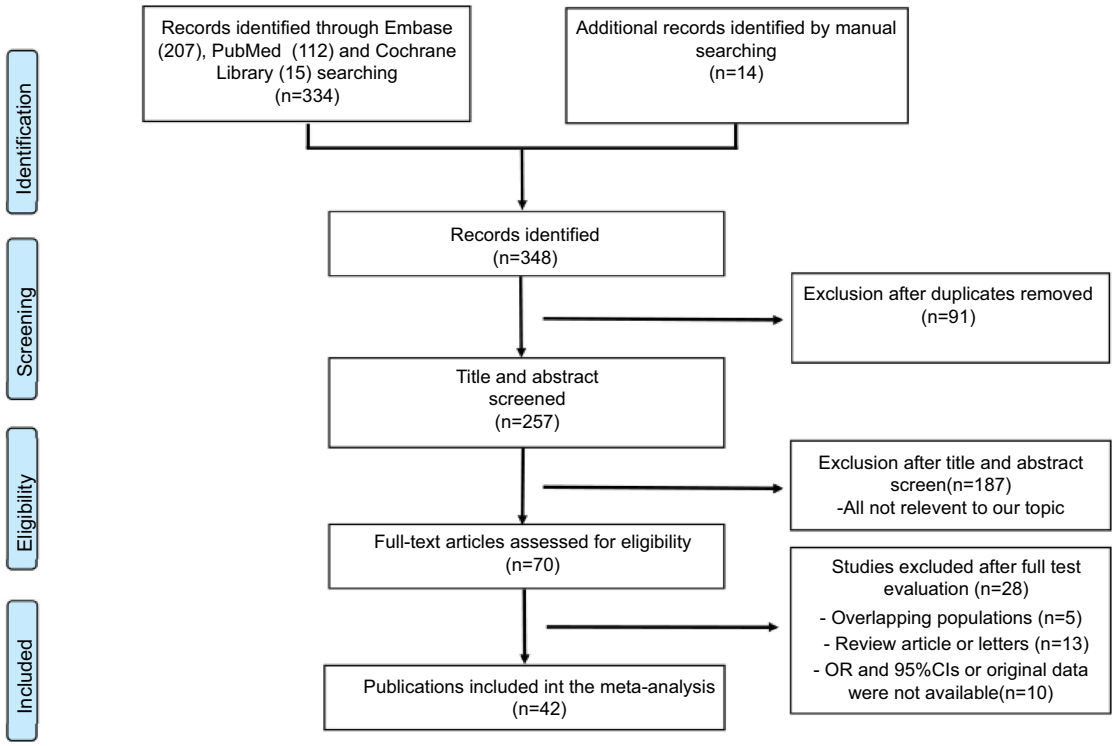


Figure 1 PRISMA flow chart.

revealed that P53 overexpression (OR 3.57, 95% CI 1.93–6.62; $p<0.001$) is a significant predictor of LNM (Figure 2C).

Ki-67 and HPV infection status

Ki-67 overexpression as a predictor of LNM was reported in three studies. Heterogeneity was observed between the studies ($I^2=55\%$; $p=0.11$). Cumulative analysis of these data revealed that Ki-67 overexpression (OR 2.70, 95% CI 0.81–9.05; $p=0.110$) is not a significant predictor of LNM (Figure 2D). Six studies reported the association between HPV infection and LNM, in which 208 (42%) and 285 (58%) patients had positive and negative HPV infection, respectively. No heterogeneity was noted between the studies ($I^2=0\%$; $p=0.49$); Cumulative analysis of these homogeneous data demonstrated that HPV infection (OR 0.85, 95% CI 0.58–1.25; $p=0.410$) is not a significant predictor of LNM (Figure 2E).

Clinicopathological predictors for LNM

Histopathological type and growth pattern

Histopathological type as a predictor of LNM was reported in six studies; no heterogeneity between the studies was noted ($I^2=0\%$). Accumulative analysis of these homogeneous data revealed that high-risk type (OR 14.63, 95% CI 6.40–33.42; $p<0.001$) and intermediate-risk type (OR 3.37, 95% CI 1.97–5.74; $p<0.001$) are significant predictors of LNM compared with low-risk type (Figure 3A). Three studies reported growth pattern-related LNM risk, which included 398 patients (vertical pattern 149 vs superficial pattern 149). Cumulative analysis of homogeneous data demonstrated that vertical growth pattern (OR 1.97, 95% CI 1.13–3.43; $p=0.020$) is a significant predictor of LNM (Figure 3B).

Tumor stage: AJCC and UICC TNM stage system

Eight studies adapted the AJCC TNM system. We performed a subgroup analysis based on different versions (1997, 2002, 2010, and 2016). Heterogeneity of each subgroup was acceptable. Pooled results of all subgroups demonstrated that higher stage was a significant predictor of LNM (Figure 4). Thirteen studies adapted the UICC TNM system. Similarly, pooled results of subgroups demonstrated the same conclusion.

Tumor grade and tumor size

Among the 2,680 patients from 25 studies with ORs for tumor grade-related LNM risk, 1,652 (62%) and 1,028 (38%) had high-grade (G2, G3) and low-grade (G1) penile cancer, respectively. Accumulative analysis of available ORs

Table 1 Characteristics of included studies

Studies (year)	Country	No. of patients	Median age, years (range)	No. of LNM	Median follow-up, Mo (range)	Included predictors	NOS score
Alkatout et al 2011[21]	Germany	72	64 (34–91)	34	35 (0–142)	Clinical lymph node, stage, grade, growth pattern, LVI	8
Azizi et al 2018[24]	America	68	65 (53–69)	45	36 (19–90)	Clinical lymph node, LVI, NLR	8
Bhagat et al 2010[25]	India	53	50 (27–74)	22	19 (9–65)	Age, clinical lymph node, stage, grade, LVI, invasion depth	6
Chalya et al 2015[26]	Tanzania	236	47 (21–78)	154	22 (3–61)	Grade, histopathological type, tumor size, LVI, urethra invasion	6
Chen et al 2012[27]	China	56	53.42 (NR)	14	27 (17–43)	Stage, grade	6
Cubilla et al 2001[28]	America	61	NR	20	NR	Histopathological type	6
Dai et al 2006[29]	China	72	51 (27–81)	23	NR	Stage, grade, histopathological type	7
Emerson et al 2001[30]	America	20	63 (40–81)	8	28 (4–99)	Stage, grade, histopathological type	6
Ficarra et al 2005[31]	Italy	175	62 (34–91)	71	NR	Age, clinical lymph node, stage, grade, tumor size, growth pattern, LVI, vascular invasion, lymphatic invasion, corpora cavernosa invasion, corpus spongiosum invasion, urethra invasion	9
Fonseca et al 2013[32]	Brazil	82	58 (22–91)	46	20 (1–71)	Stage, grade, LVI, nerve invasion, HPV infection	8
Ghazal et al 2013[23]	Germany	51	63 (33–88)	16	27 (NR)	Stage, grade	8
Graafland et al 2010[33]	Netherlands	342	65 (26–96)	68	32 (3–91)	Grade, corpora cavernosa invasion, corpus spongiosum invasion, LVI, urethra invasion	9
Guimares et al 2007[35]	Brazil	125	NR	55	33 (1–453)	Age, race, clinical lymph node, stage, grade, LVI, corpora cavernosa invasion, Ki-67	8
Guimares et al 2009[34]	Brazil	333	NR	81	100 (1–453)	Histopathological type	7
Gunia et al 2012[36]	Germany	92	NR	19	NR	P53	6
Hall et al 1998[37]	America	46	NR	14	NR	Stage, grade, invasion depth	6
Harmaya et al 2017[38]	Indonesia	50	NR	25	NR	Age, stage, grade, vascular invasion	6
Kroon et al 2008[40]	Netherlands	56	NR	32	NR	Stage, grade, vascular invasion	7
Lopes et al 1996[44]	Brazil	145	53 (26–79)	76	33 (1–453)	Age, race, clinical lymph node, stage, grade, lymphatic invasion, invasion depth, corpora cavernosa invasion, corpus spongiosum invasion, urethra invasion, HPV infection	8
Lopes et al 2002[43]	Brazil	82	52 (27–77)	42	89 (1–453)	P53	7
Mannweiler et al 2013[45]	Austria	72	NR	8	47 (5–265)	Clinical lymph node, growth pattern, lymphatic invasion, urethra invasion, invasion depth, HPV infection	8
Ornellas et al 2008[46]	Brazil	196	57 (25–98)	70	74 (1–93)	Stage, grade, invasion depth, LVI, corpora cavernosa invasion, corpus spongiosum invasion, urethra invasion, nerve invasion	8
Protzel et al 2007[47]	Germany	28	69 (35–89)	16	46 (2–105)	Clinical lymph node, stage, grade, Ki-67, HPV infection	7
Qu et al 2018[48]	Canada	380	66 (29–99)	63	54 (0–131)	Age, stage, grade, vascular invasion, histopathological type	9
Slaton et al 2001[50]	America	48	51 (26–81)	18	73 (23–154)	Stage, grade, invasion depth, vascular invasion	8
Termini et al 2015[52]	Brazil	125	NR	44	NR	Age, clinical lymph node, stage, grade, invasion depth, vascular invasion, corpora cavernosa invasion, corpus spongiosum invasion, urethra invasion, nerve invasion, HPV infection	6

(*Continued*)

Table 1 (Continued).

Studies (year)	Country	No. of patients	Median age, years (range)	No. of LNM	Median follow-up, Mo (range)	Included predictors	NOS score
Theodorescu et al 1996[53]	America	42	62 (22–84)	26	42 (1–168)	Age, grade, tumor size	7
Velazquez et al 2008[56]	Paraguay	134	55 (24–82)	66	NR	Grade, nerve invasion,	5
Wang et al 2018[5]	China	198	53 (20–84)	96	NR	Age, clinical lymph node, stage, grade, invasion depth, LVI, nerve invasion, histopathological type	9
Winters et al 2016[57]	America	461	62 (52–71)	111	NR	Stage, grade, LVI	9
Zargar-Shoshtari et al 2015[59]	America	57	60 (53–73)	31	22 (NR)	Race, stage, grade, LVI, HPV infection, P53	7
Li et al 2016[42]	China	124	50 (25–86)	60	NR	CRP, SCC-Ag	7
Steffens et al 2013[22]	Germany	79	65.2 (33–92)	16	23 (NR)	CRP	7
Kasuga et al 2016[51]	Japan	41	69 (68.5 ±11.8)	9	34.7 (2.3–271.7)	NLR	6
Hungerhuber et al 2007[39]	Germany	24	NR	16	NR	SCC-Ag	6
Touloupidis et al 2007[54]	Greece	16	NR	7	48 (24–84)	SCC-Ag	6
Laniado et al 2003[41]	British	11	NR	7	36 (NR)	SCC-Ag	6
Deng et al 2016[58]	China	116	53 (24–86)	42	NR	PD-L1	8
Udager et al 2016[55]	America	37	NR	11	NR	PD-L1	7
Ottenhof et al 2018[49]	Netherlands	213	NR	68	100.7 (69.4–119.7)	PD-L1	8
Zhu et al 2007[61]	China	73	55 (27–75)	30	NR	Stage, grade, Ki-67,	8
Zhu et al 2010[60]	China	110	54 (20–75)	26	NR	LVI, P53	8

Abbreviations: LNM, lymph node metastasis; NOS, Newcastle–Ottawa quality assessment scale; LVI, lymphovascular invasion; HPV, human papillomavirus; NR, not reported; PD-L1, program death ligand 1; SCC-Ag, squamous cell carcinoma antigen; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

Table 2 Pooled results of predictors for LNM

Predictors	No. of studies	No. of patients (pre/non-pre)	Pooled OR [95%CI]	p	I^2 (%)	Effects model
Tumor size	4	NR	2.00 [1.29–3.10]	0.002	0	Fixed
Vertical growth pattern	3	149/149	1.97 [1.13–3.43]	0.02	0	Fixed
Histopathological type[a]	6	63/178	14.63 [6.40–33.42]	<0.001	0	Fixed
Histopathological type[b]	6	799/178	3.37 [1.97–5.74]	<0.001	0	Fixed
Higher tumor stage[c]	8	757/431	3.66 [2.47–5.42]	<0.001	50	Fixed
Higher tumor stage[d]	13	800/371	2.43 [1.80–3.26]	<0.001	0	Fixed
Higher tumor grade	25	1652/1028	3.37 [2.38–4.78]	<0.001	59	Random
Lymphovascular invasion	18	490/1638	3.37 [2.72–4.16]	<0.001	0	Fixed
Invasion depth	6	408/144	2.58 [1.42–4.64]	0.002	38	Fixed
Corpora cavernosa invasion	6	385/630	2.22 [1.63–3.04]	<0.001	0	Fixed
Corpus spongiosum invasion	5	430/370	1.73 [1.22–2.46]	<0.001	0	Fixed
Urethra invasion	7	204/763	1.81 [1.07–3.05]	0.03	59	Random
Nerve invasion	7	196/670	2.84 [1.99–4.04]	<0.001	7	Fixed
PD-L1	3	NR	2.55 [1.40–4.64]	0.002	2	Fixed
P53	4	111/165	3.57 [1.93–6.62]	<0.001	0	Fixed
SCC-Ag	4	85/90	8.52 [4.09–17.78]	<0.001	0	Fixed
CRP	2	69/119	4.78 [2.48–9.20]	<0.001	0	Fixed
NLR	2	58/51	4.22 [1.36–13.09]	0.01	0	Fixed
Ki-67	3	112/106	2.70 [0.81–9.05]	0.11	55	Random
Race	3	72/255	0.92 [0.52–1.63]	0.77	0	Fixed
Age	9	NR	0.99 [0.95–1.03]	0.65	29	Fixed
Positive HPV infection	6	208/285	0.85 [0.58–1.25]	0.41	0	Fixed

Notes: [a]High-low risk group and [b]Intermediate-low risk group. [c]AJCC TNM stage system and [d]UICC TNM stage system.
Abbreviations: LNM, lymph node metastasis; OR: odds ratio; CI, confidence intervals; I^2, the heterogeneity between studies; pre, predictors; NR, not reported; PD-L1, program death ligand 1; SCC-Ag, squamous cell carcinoma antigen; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

demonstrated that high tumor grade (univariable subgroup: OR 3.47, 95% CI 2.26–5.32; $p<0.001$; multivariable subgroup: OR 3.27, 95% CI 2.14–5.01; $p<0.001$) is a significant predictor of LNM (Figure 5A). Heterogeneity between the studies in univariable subgroup was significant ($I^2=64\%$; $p<0.001$); tumor size as a predictor of LNM was reported in four studies. They used 3 cm as the cutoff value. No heterogeneity between the studies ($I^2=0\%$; $p=0.55$) was found, and cumulative analysis of homogeneous data revealed that tumor size (>3 cm) (OR 2.00, 95% CI 1.29–3.10; $p=0.002$) is a significant predictor of LNM (Figure 5B).

Lymphovascular invasion, invasion depth, and nerve invasion

Among the 2,128 patients from 18 studies with ORs for LVI–related LNM risk, 490 (23%) and 1,638 (77%) had positive LVI and negative LVI, respectively. No between-study heterogeneity was observed in the two subgroups. Accumulative analysis of available ORs revealed that LVI (univariable subgroup: OR 4.44, 95% CI 3.12–6.31; $p<0.001$; multivariable subgroup: OR 2.88, 95% CI 2.20–3.75; $p<0.001$) is a significant predictor of LNM (Figure 6A). Invasion depth as a predictor of LNM was reported in six studies. They used 5 mm as the cutoff value. Moderate heterogeneity was observed between the studies ($I^2=38\%$; $p=0.15$); Cumulative analysis of the ORs revealed that invasion depth (>5 mm) (OR 2.58, 95% CI 1.42–4.69; $p=0.002$) is a significant predictor of LNM (Figure 6B). Nerve invasion as a predictor of LNM was reported in seven studies, in which 196 (23%) and 670 (77%) patients had positive and negative nerve invasion, respectively. No heterogeneity was noted between the studies ($I^2=7\%$; $p=0.37$). Cumulative analysis of these homogeneous data revealed that nerve invasion (OR 2.84, 95% CI 1.99–4.04; $p<0.001$) is a significant predictor of LNM (Figure 6C).

Cavernosum invasion, urethra invasion, age, and race

Six studies reported the association between corpora cavernosum invasion and LNM. The data were homogeneous ($I^2=0\%$; $p=0.900$) and cumulative results demonstrated that corpora cavernosum invasion (OR 2.22, 95% CI 1.63–3.04; $p<0.001$) is a significant predictor of LNM (Figure 7A). Similarly, cumulative analysis revealed that

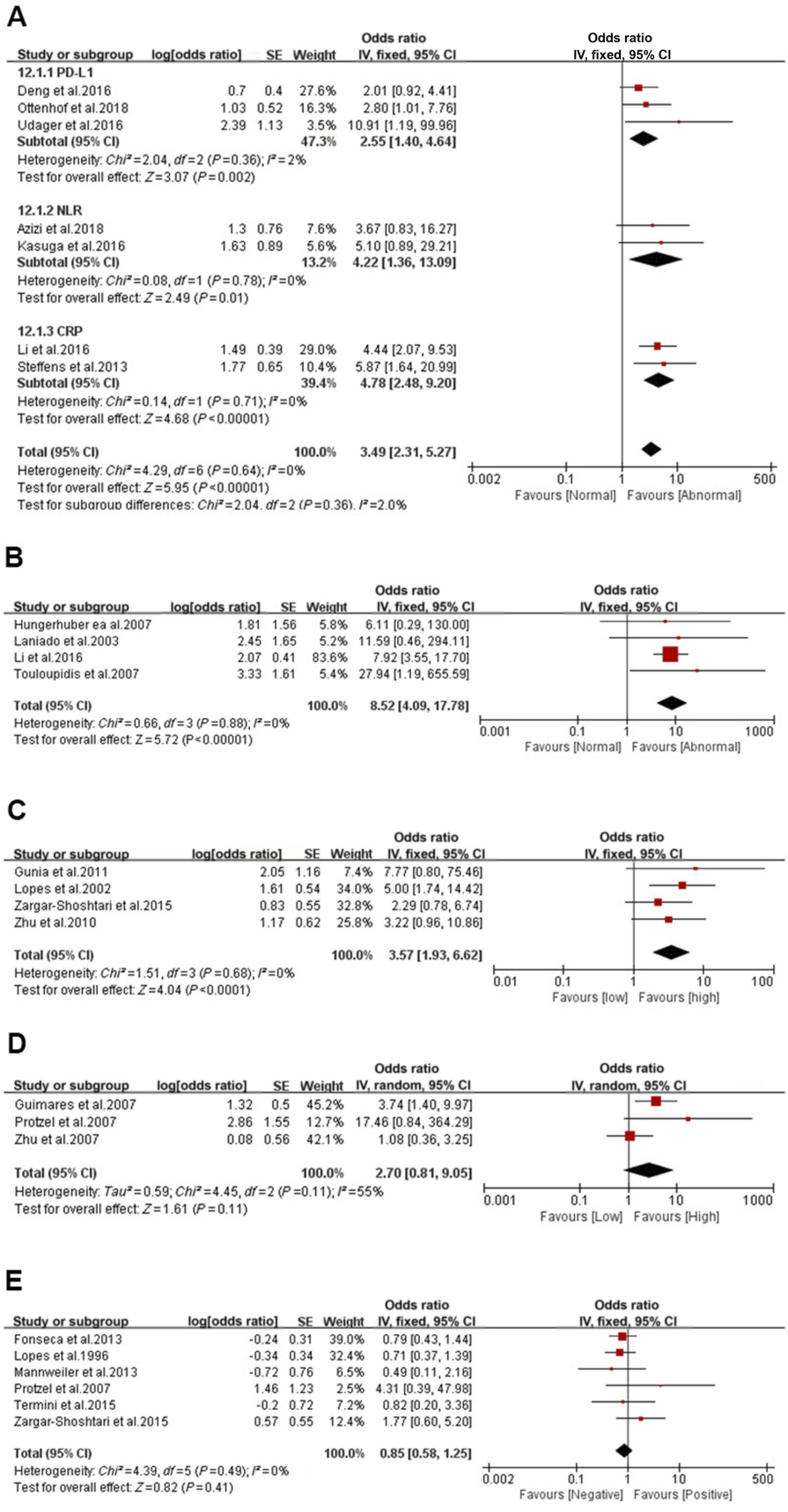


Figure 2 Forest plots of biomarker-specific predictors. (**A**) Immune-related predictors. (**B**) SCC-Ag. (**C**) P53 protein. (**D**) Ki-67. (**E**) HPV infection.

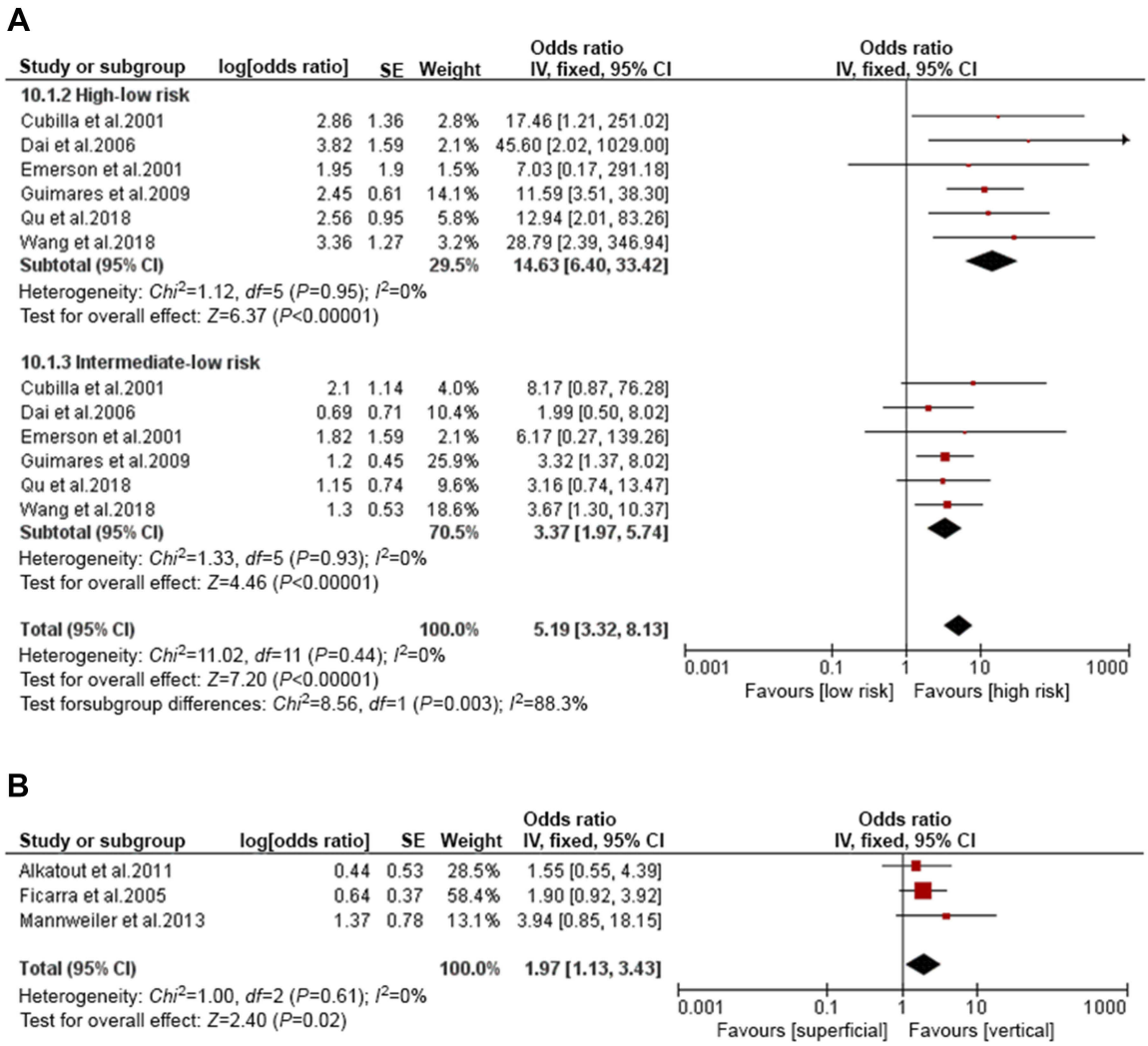


Figure 3 Forest plots of histopathological type , growth pattern. . (**A**) Histopathological type. (**B**) Growth pattern.

corpus spongiosum invasion (OR 1.73, 95% CI 1.22–2.46; p=0.002) is also a significant predictor of LNM (Figure 7B). Seven studies reported the association between urethra invasion and LNM. Pooled results demonstrated that urethra invasion (OR 1.81, 95% CI 1.07–3.05; p=0.030) is a significant predictor of LNM (Figure 7C). Heterogeneity was observed between included studies (I^2=59%; p=0.02); Nine studies reported the association between age and LNM. Heterogeneity was moderate (I^2=29%; p=0.19); Cumulative analysis of available ORs demonstrated that age (OR 0.99, 95% CI 0.95–1.03; p=0.65) was not a significant predictor of LNM (Figure 7D). Three studies reported the race-related LNM risk. Accumulative analysis of these homogeneous data revealed that race (OR 0.92, 95% CI 0.52–1.63; p=0.77) was not a significant predictor of LNM (Figure 7E).

Discussion

The effectiveness of current guidelines in managing inguinal lymph nodes of patients with penile cancer had been challenged by a prospective study.[62] This prospective study revealed that over 80% of the patients, who were categorized as intermediate or high risk for developing LNM according to the current guidelines, accepted unnecessary prophylactic ILND. This inaccuracy may be caused by the small number of predictors included in the current guidelines. In addition, ILND exhibits serious surgical complications. To pinpoint patients who are the best candidates for receiving radical ILND, we conducted this comprehensive meta-analysis. Consequently, we identified numerous valuable predictors which could be classified into two categories, including tumor-associated biomarkers and invasive clinicopathologic characteristics. To

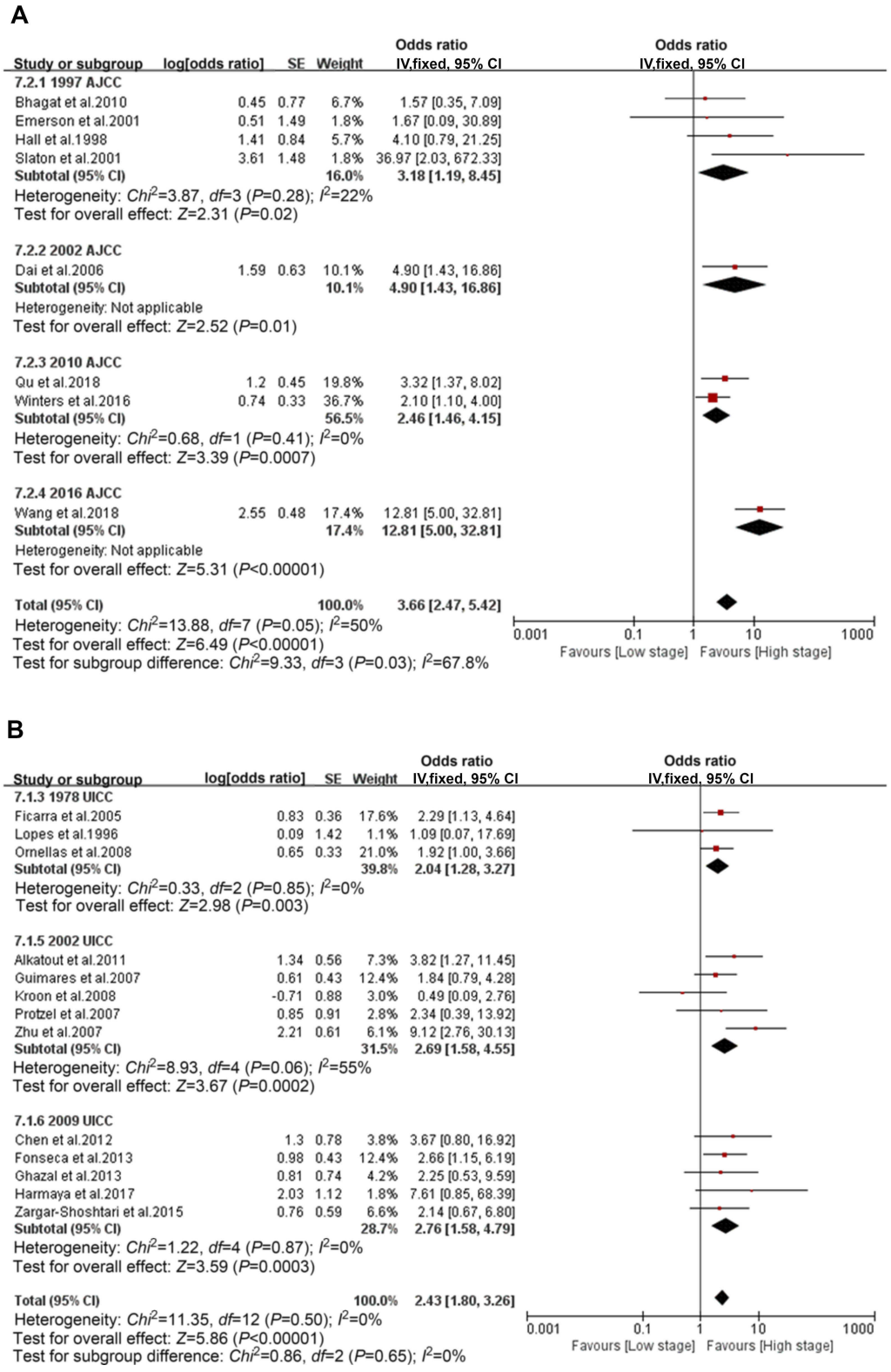


Figure 4 Forest plots of different TNM systems. (**A**) American Joint Commission on Cancer (AJCC) TNM stage system. (**B**) Union for International Cancer Control (UICC) TNM stage system.

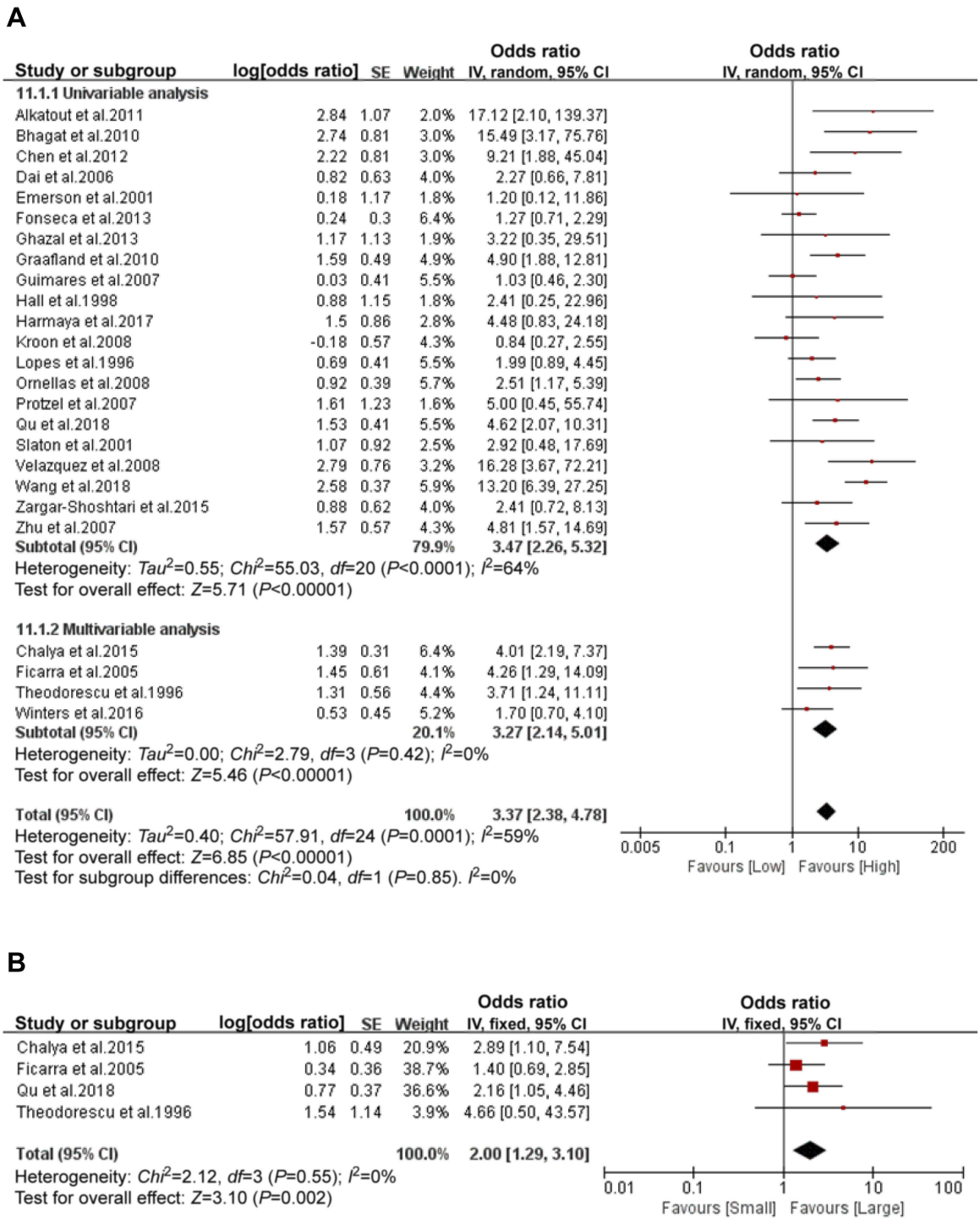


Figure 5 Forest plots of tumor grade and size. (**A**) Tumor grade. (**B**) Tumor size.

our knowledge, this meta-analysis is the first to combine comprehensive and detailed evidence on extensive potential predictors of LNM for patients with penile cancer.

It is well established that inflammation contributes a lot to the initiation and progression of cancers.[63] Several immune-related predictors, such as NLR, CRP, and PD-L1, were conclusively identified in this meta-analysis. NLR combining of neutrophilia and lymphopenia represents systemic inflammatory response and immune response. It is an independent predictor of poor prognosis for several solid cancers including

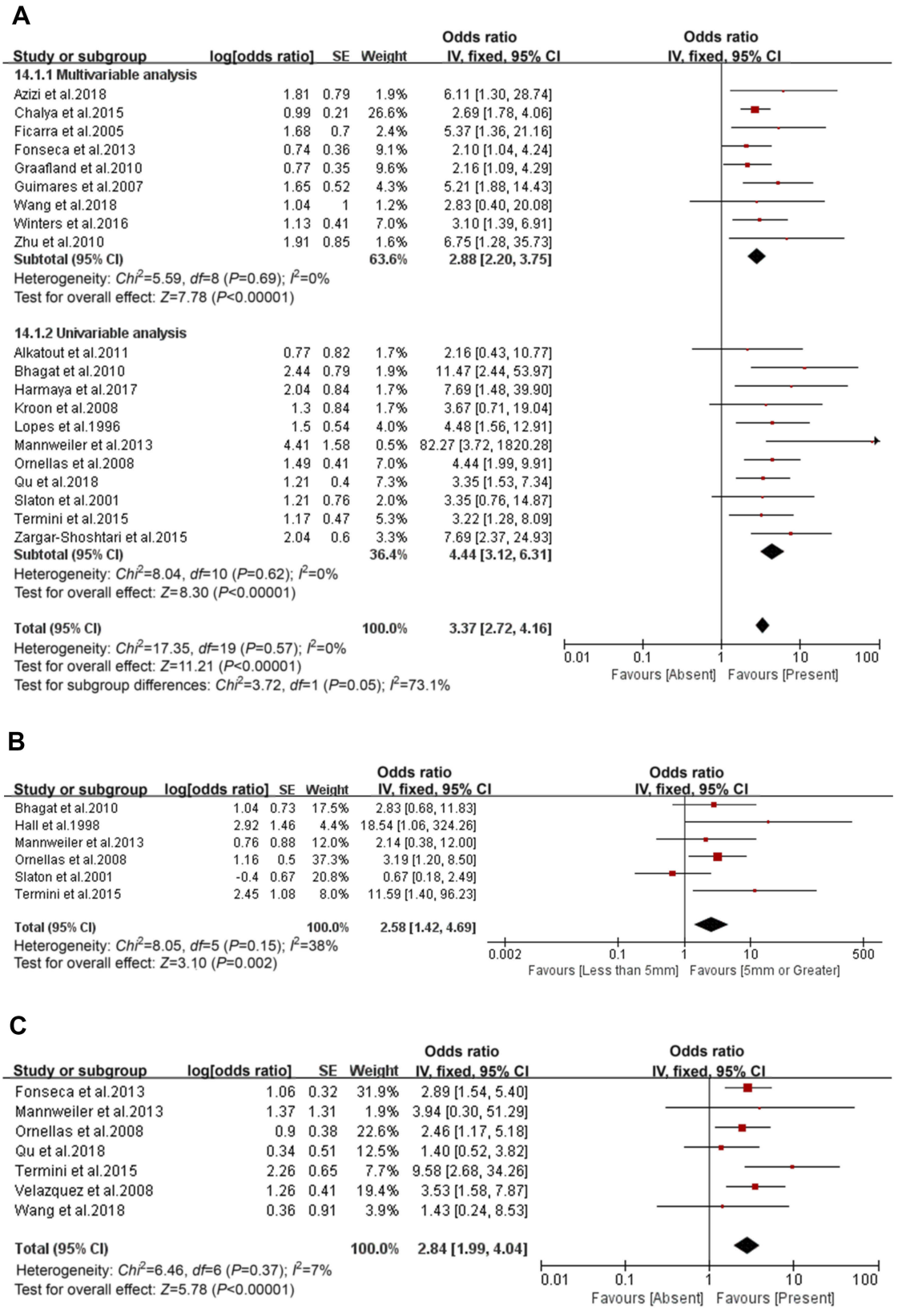


Figure 6 Forest plots of lymphovascular invasion, invasion depth and nerve invasion. (**A**) Lymphovascular invasion (LVI). (**B**) Invasion depth. (**C**) Nerve invasion.

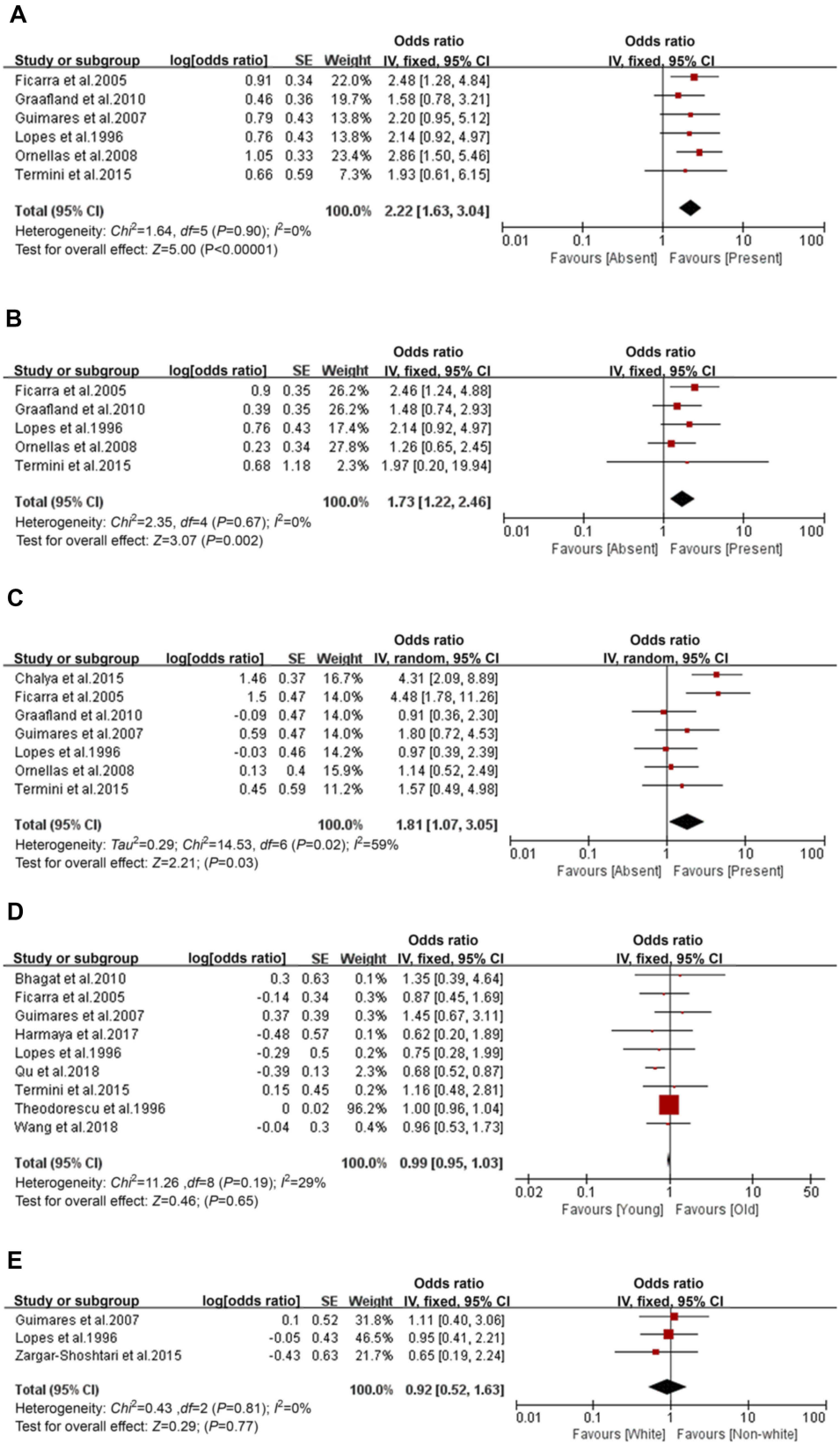


Figure 7 Forest plots of corpora cavernosa invasion, corpus spongiosum invasion, urethra invasion, age and race. (**A**) Corpora cavernosa invasion. (**B**) Corpus spongiosum invasion. (**C**) Urethra invasion. (**D**) Age. (**E**) Race.

castration-resistant prostate cancer, cervical adenocarcinoma, lung cancer, and esophageal carcinoma.[64–67] Similarly, a study enrolling 84 consecutive penile cancer patients investigated the association between NLR with pathologic LNM and prognosis.[24] This study demonstrated that NLR was an independent predictor of overall survival. In addition, patients with an elevated NLR were related to higher risk of pathologic LNM, although this relationship was not significant in adjusted analysis. CRP is an acute-phase protein produced almost exclusively by the liver. Its prognostic value for patients with penile cancer has been demonstrated.[22,42] According to the I^2 statistics, there was no heterogeneity for these biomarkers between included studies. Furthermore, both NLR and CRP are measured easily and economically in clinical practice. These features may facilitate the clinical application of these two biomarkers.

Another important and therapeutic potential biomarker is PD-L1, a transmembrane protein with the ability to suppress host immune system. It is a critical component of tumor-specific immune resistance mechanisms.[68] Cancer immunotherapy by targeting PD-L1 can improve overall survival for patients with advanced cancer.[69] However, evidence on cancer immunotherapy for patients with penile cancer is limited. One target of this meta-analysis was to investigate the association between PDL-1 with inguinal LNM and prognosis in populations with penile cancer. We revealed that higher PD-L1 expression in tumor cells was related to higher risk of LNM and poorer prognosis. This conclusion, to some extent, provided a theoretical basis for the application of targeted anti-PD-L1 immunotherapy in penile cancer patients.

SCC-Ag, a tumor-associated glycoprotein, is bound up with early recurrence of cervical cancer.[70] However, its relationship with early recurrence and risk of LNM in patients with penile cancer has not been summarized. Touloupidis et al revealed elevated SCC-Ag level predicted LNM and distant metastasis.[54] Laniado et al demonstrated elevated SCC-Ag level had a high specificity (100%) and an intermediate sensitivity (57%) for prediction of LNM.[41] However, Hungerhuber et al found that it was just related to tumor burden rather than LNM.[39] Based on an accumulate meta-analysis of these discrepant data, we conclusively demonstrated that elevated SCC-Ag was a predictor of LNM. However, due to the small sample size of prior studies, the clinical application of SCC-Ag to predict LNM should be further validated by more large-scale researches.

For these biochemical predictors, given the limited number of included studies, we are unable to perform subgroup analysis based on different cut-off points, different antibodies, or different measurement methods. This accounted for the cross-study heterogeneity. Meanwhile, there are other immune biomarkers, such as CD8, CD163, and so on. However, we cannot include them in this meta-analysis because of insufficient data. This may be a direction of our future research.

Two TNM stage systems consisting of AJCC and UICC were adapted for penile cancer in this meta-analysis and they are constantly updated. Therefore, we performed a subgroup analysis based on different TNM versions. No matter which version we analyzed, we found that patients with higher stage disease were at higher LNM risk. In addition, we further analyzed all components of these TNM systems as well as other common pathological characters. Conclusively, the LNM risk will increase significantly as long as there is any invasive pathological character, such as LVI, corpora cavernosum invasion, corpus spongiosum invasion, urethra invasion, nerve invasion, larger tumor size, and deeper tumor invasion.

A large-scale study performed by Wang et al showed that LNM rates ranged from 5% to 100% between different risk stratified histological subtypes.[5] This huge risk difference highlighted the importance of a conclusive histological risk stratification. Therefore, we divided patients into three risk groups (high-risk, intermediate-risk, and low-risk groups) and compared the LNM risk between each group. Results suggested that this risk stratification was viable. Patients with high-risk histological subtype (basaloid, sarcomatoid, adenosquamous, and poorly differentiated types) were at obviously higher LNM risk.

For patients with cN+, the LNM risk ranged from 54% to 85% (mean 62%) in these included studies. Results of all individual studies were statistically significant. For tumor grade, we performed subgroups analysis based on multivariable and univariable analysis. Both groups demonstrated that higher grade was related to higher LNM risk. Similarly, such a positive correlation was also revealed between tumor vertical growth pattern and LNM risk. However, we did not find any correlation between LNM risk and age, race or HPV infection.

This study has several limitations. First, we failed to analyze some important factors, such as the tumor site, tumor multifocality, tumor cell keratinization, and koilocytosis. Second, some studies only provided original statistical data rather than direct ORs. Third, several methodological drawbacks of the included studies were noted, such as the small series, single-center and retrospective nature of these

studies. Fourth, the number of studies focusing on biomarkers was small, and some other important biomarkers were not included due to insufficient data. Given these drawbacks, high-quality studies are warranted to further validate our conclusion. In addition, future studies should explore the intrinsic links between these predictors and then create an accurate and comprehensive mathematical predictive model for LNM by integrating multiple predictors.

Conclusion

We identified valuable predictors of LNM in penile cancer patients, such as tumor-associated biomarkers (NLR, CRP, PD-L1, SCC-Ag, and P53 protein) and invasive clinicopathologic characteristics (higher stage, LVI, cavernosum invasion, urethra invasion, nerve invasion, deeper invasion, cN+, larger tumor size, higher grade, vertical growth pattern, and high- and intermediate-risk histopathological subtype).

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Disclosure

The authors report no conflicts of interest in this work.

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