A Systematic Review and Meta-Analysis of Variant Histology in Urothelial Carcinoma of the Bladder Treated with Radical Cystectomy

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Purpose: The currently available evidence regarding the prognostic and clinical significance of each variant histology subtype of urothelial bladder cancer remains scarce. We assessed the prognostic value of variant histology in patients with urothelial carcinoma of the bladder treated with radical cystectomy.

Materials and Methods: PubMed®, Web of Science™, Cochrane Library and Scopus® databases were searched for articles published before October 2019 according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. We identified 39 studies comprising 20,544 patients matching our eligibility criteria.

Results: Studies were deemed eligible if they compared overall, cancer specific and recurrence-free survival in patients with urothelial carcinoma of the bladder with and without variant histology. Formal meta-analyses were performed for these outcomes. Variant histology was associated with worse cancer specific (pooled HR 1.37, 95% CI 1.24–1.50), overall (pooled HR 1.44, 95% CI 1.26–1.65) and recurrence-free survival (pooled HR 1.32, 95% CI 1.20–1.45). Subgroup analyses demonstrated that "micropapillary" (pooled HR 1.20, 95% CI 1.02–1.41), "plasmacytoid" (pooled HR 2.03, 95% CI 1.17–3.52) and "small cell" variant histology (HR 3.32, 95% CI 1.98–5.59) were also associated with worse overall survival.

Conclusions: Variant histology in patients with urothelial carcinoma of the bladder is associated with increased risks of disease recurrence as well as cancer specific and overall mortality. Variant histology was independently associated with overall survival in the "micropapillary," "plasmacytoid" and "small cell" subgroups. Variant histology should be integrated into prognostic tools to guide risk stratification, treatment planning and patient counseling. However, caution should be exercised in interpreting the conclusions drawn from this study given the limitations, which include the heterogeneity of the population of interest and the retrospective nature of the primary data evaluated.

Key Words: urinary bladder neoplasms, meta-analysis, cystectomy, histology

Abbreviations and Acronyms

AC = adjuvant chemotherapy
CSS = cancer specific survival
NAC = neoadjuvant chemotherapy
OS = overall survival
PLND = pelvic lymph node dissection
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUCB = pure urothelial carcinoma of the bladder
RC = radical cystectomy
RFS = recurrence-free survival
RoB = risk of bias
UC = urothelial carcinoma
UCB = urothelial carcinoma of the bladder
VH = variant histology

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Urothelial carcinoma of the bladder is the ninth most commonly diagnosed cancer worldwide.[1] Radical cystectomy with pelvic lymph node dissection is the mainstay of treatment for muscle invasive disease.[2–4] However, despite definitive therapy, the 5-year overall survival of patients undergoing radical cystectomy remains below 60%.[5,6] Thus, various clinical and pathological factors have been identified to improve risk stratification of patients with urothelial carcinoma of the bladder with the aim to facilitate clinical decision making and patient counseling.[7–9] Variant histology has been identified as a key pathological feature that reflects the biology and clinical behavior of individual urothelial carcinomas of the bladder.[10,11]

UC is the most common histological type of bladder cancer, accounting for nearly 90% of all bladder tumors.[1,12] UC exhibits morphological and clinical diversity. To a degree, it appears that these variables are somewhat related, allowing inferences regarding clinical outcomes to be made from the morphological subtype of an individual neoplasm, thereby facilitating therapeutic planning.[13] Previous studies have shown that VH is associated with advanced tumor stage, extravesical disease and lymph node invasion.[11,14–17] Indeed, the majority of the literature suggests that VH is an unfavorable prognostic factor. Conversely some data suggest that VH does not significantly affect oncologic outcomes compared to PUCB.[15,17–19] Moreover, the currently available evidence regarding the prognostic and clinical significance of each VH subtype is scarce. We performed this systematic review to summarize the current data and to determine whether VH type can aid in the prognostication of UCB cases.

MATERIALS AND METHODS

This study is registered with the International Prospective Register of Systematic Reviews (CRD42020150676, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42020150676).

Search Strategy

The systematic review was performed according to the PRISMA statement.[20] A completed PRISMA 2009 checklist is provided in supplementary table 1 (https://www.jurology.com). PubMed, Web of Science, Cochrane Library and Scopus databases were searched to identify reports published before October 2019 regarding the prognostic value of VH in UCB. The following keywords were used: (bladder cancer OR bladder carcinoma OR urothelial carcinoma OR urothelial cancer) AND (difference OR variant OR differentiation OR VH OR CVH) AND (multivariable OR multivariate). The primary outcome was cancer specific survival, and the secondary outcomes were overall and recurrence-free survival.

Initial screening was performed independently by 2 investigators based on the titles and abstracts to identify ineligible reports. Potentially relevant reports were subjected to a full text review, and the relevance of the reports was also confirmed after the data extraction process.

Inclusion and Exclusion Criteria

Studies were included if they investigated patients with UCB with VH ("patients") who had undergone RC ("intervention") compared to those without VH ("comparison") to assess the prognostic impact of VH on cancer specific, overall and recurrence-free survival ("outcome") using multivariable Cox regression analysis ("study design") in nonrandomized observational, randomized or cohort studies. There was no restriction imposed on disease stage, extent of PLND or implementation of neoadjuvant chemotherapy/adjuvant chemotherapy in selecting the population of interest. We excluded reviews, letters, editorials, meeting abstracts and case reports. In cases of multiple publications on the same cohort either the higher quality or the most recent publication was selected. References of included articles were scanned for additional studies of interest.

Data Extraction

Two investigators independently extracted the following information: first author name, publication year, recruitment region, period of patient recruitment, number of patients, age, gender, study design, pathological TN stage, oncologic outcomes, followup duration, conclusion, and VH number and type. Subsequently the hazard ratios and 95% confidence intervals associated with each outcome were retrieved. HRs were extracted from multivariate analyses.

Quality Assessment

The Newcastle-Ottawa Scale was used to assess the quality of the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[21,22] The scale rates 3 factors, ie selection, comparability and exposure, with total scores ranging from 0 (lowest) to 9 (highest). The main confounders were identified as the important prognostic factors of oncologic outcomes. The presence of confounders was determined by consensus and review of the literature. We defined studies with scores greater than 6 as "high quality."

Risk of Bias Assessment

The risk of bias evaluation of each study was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. Due to only nonrandomized comparative studies, RoB was determined by examining the risk of preassigned confounders. The confounding factors were identified as the most important prognostic factors at the time of treatment. The articles were therefore reviewed based on the adjustment for the effects of age, gender, tumor staging and grading, positive surgical margins, lymphovascular invasion and receipt of perioperative chemotherapy. The RoB of each study was assessed independently by 2 authors. The overall RoB level was judged as "low," "intermediate" or "high" (supplementary fig. 1, https://www.jurology.com).

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Statistical Analyses

Forest plots were used to assess multivariate HRs and to obtain summary HRs to describe the relationships between VH and overall, cancer specific and recurrence-free survival. Disease recurrence was defined as tumor relapse in the operative field, regional lymph node involvement and/or distant metastasis. RFS did not include intravesical tumor recurrence as an event in the analysis. In addition, VH was defined as nonpure UC, including UC with VH or pure VH in this analysis. Studies were considered in the meta-analysis only if they used a multivariable Cox proportional hazards regression model. In studies with only HRs and p values we calculated the corresponding 95% CIs.[23,24] We also performed subgroup analyses of "micropapillary" (including microcystic), "squamous and/or glandular" (including adenocarcinoma), "plasmacytoid" (including signet ring), "small cell" (including neuroendocrine) and "sarcomatoid" VH.

Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using the Cochrane Q-test and the I^2 statistic. Significant heterogeneity was indicated by $p < 0.05$ in the Cochrane Q-tests and I^2 greater than 50%. Random effects models were used for initial calculation of the Cochrane Q-test and the I^2 statistic. We used fixed effects models to calculate pooled HRs for nonheterogeneous results.[25–27] Publication bias was assessed with funnel plots. In the absence of publication bias the funnel would look symmetrical and cone-shaped, while in the presence of publication bias associated with nonpublication of negative results it would tend to look asymmetrical.

Sensitivity analyses were conducted to assess the robustness of the results by excluding 1 study from each analysis. These analyses were conducted to examine the impact of weighting and whether a single study was driving the conclusions. Therefore, another set of sensitivity analyses was also performed based on the quality of the studies included. All statistical analyses were performed using Stata®/MP 14.2 and statistical significance was set at $p < 0.05$.

RESULTS

Study Selection and Characteristics

Our initial search identified 2,718 publications. A total of 2,620 articles were excluded after screening the titles and abstracts, and a full text review was performed for 98 articles (fig. 1). After applying the selection criteria we identified 39 articles comprising 20,544 patients for the systematic review and meta-analysis.[15,19,28–66] Extracted data from the 39 studies are outlined in supplementary tables 2 and 3 (https://www.jurology.com).

All included studies were retrospective and were published between 2004 and 2019. Of the studies 12 were from Europe, 16 from North and South America, 7 from Asia and 4 from international collaboration. VH in the pathological specimen was reported in 2,871 of 20,544 patients (14.0%). A total of 13,359 patients (76.6%) were male and 4,072 (23.4%) were female. A total of 6,406 patients (39.9%) had stage pT3 or higher and 4,351 (25.4%) had stage pN1 or higher disease. Median patient age was 61 to 69 years and followup was 17.6 to 170.4 months. The studies had a median Newcastle-Ottawa Scale score of 7 (range 6 to 7).

Meta-Analysis

Association of VH with CSS. A total of 23 studies including 22,072 patients provided data on the association of VH with CSS. The forest plot (fig. 2) indicated that VH was significantly associated with worse CSS (pooled HR 1.37, 95% CI 1.24–1.50; $z = 6.47$). The Cochrane Q-test (chi-square 68.20, $p = 0.003$) and I^2 test (42.8%) revealed no significant heterogeneity. The funnel plot identified 6 studies over the pseudo-95% CI (supplementary fig. 2, *A*; https://www.jurology.com).

Association of VH with OS. A total of 26 studies including 28,555 patients provided data on the association of VH with OS. The forest plot (fig. 3) indicated that VH was significantly associated with worse OS (pooled HR 1.44, 95% CI 1.26–1.65; $z = 5.20$). The Cochrane Q-test (chi-square 118.66, $p = 0.000$) and I^2 test (62.1%) revealed significant heterogeneity. The funnel plot identified 11 studies over the pseudo-95% CI (supplementary fig. 2, *B*; https://www.jurology.com).

Association of VH with RFS. A total of 18 studies including 24,675 patients provided data on the association of VH with RFS. The forest plot (fig. 4) indicated that VH was significantly associated with worse RFS (pooled HR 1.32, 95% CI 1.20–1.45; $z = 5.57$). The Cochrane Q-test (chi-square 61.84, $p = 0.002$) and I^2 test (45.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (supplementary fig. 2, *C*; https://www.jurology.com).

Association of micropapillary VH with OS. Seven studies including 6,448 patients provided data on the association of micropapillary (including microcystic) VH with OS. The forest plot (fig. 5, *A*) indicated that micropapillary VH was significantly associated with worse OS (pooled HR 1.20, 95% CI 1.02–1.41; $z = 2.20$). The Cochrane Q-test (chi-square 9.39, $p = 0.153$) and I^2 test (36.1%) revealed no significant heterogeneity. The funnel plot identified 1 study over the pseudo-95% CI (supplementary fig. 3, *A*; https://www.jurology.com).

Association of squamous and/or glandular VH with OS. Six studies including 5,170 patients provided data on the association of squamous and/or glandular VH with OS. The forest plot (fig. 5, *B*) indicated that squamous and/or glandular VH was not significantly associated with worse OS (pooled HR 1.23, 95% CI 0.93–1.62;

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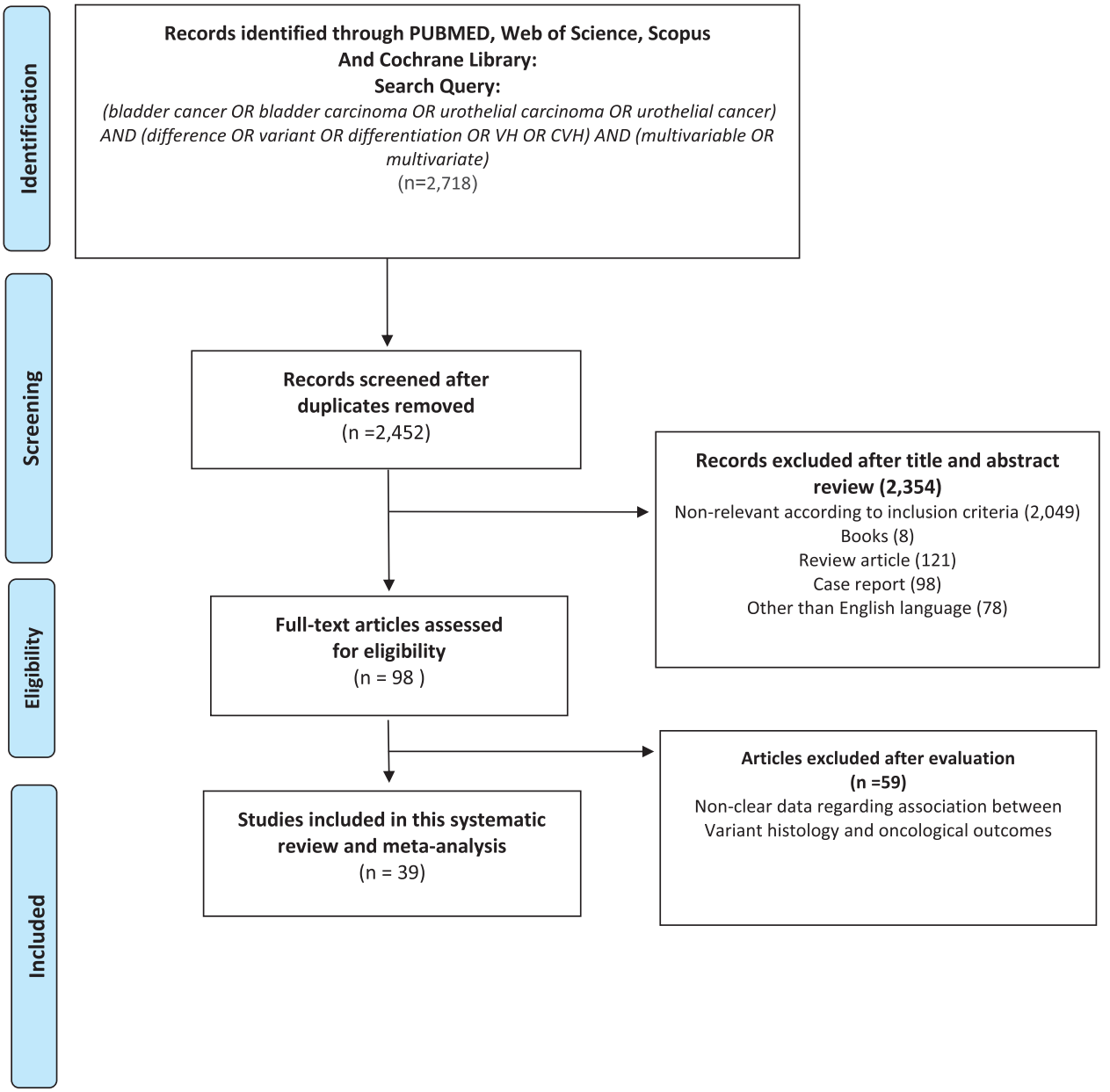

Figure 1. PRISMA flow chart outlines article selection process. Studies assessing prognostic value of variant histology in urothelial carcinoma of bladder were included.

z=1.44). The Cochrane Q-test (chi-square 15.66, p=0.028) and I^2 test (55.3%) revealed significant heterogeneity. The funnel plot identified 2 studies over the pseudo-95% CI (supplementary fig. 3, *B*; https://www.jurology.com).

Association of plasmacytoid VH with OS. Five studies including 2,977 patients provided data on the association of plasmacytoid (including signet ring) VH with OS. The forest plot (fig. 5, *C*) indicated that plasmacytoid VH was significantly associated with worse OS (pooled HR 2.03, 95% CI 1.17–3.52; z=2.53). The Cochrane Q-test (chi-square 13.02, p=0.011) and I^2 test (69.3%) revealed significant heterogeneity. The funnel plot identified 1 study over the pseudo-95% CI (supplementary fig. 3, *C*; https://www.jurology.com).

Association of sarcomatoid VH with OS. Three studies including 2,121 patients provided data on the association of sarcomatoid VH with OS. The forest plot (fig. 6, *A*) indicated that sarcomatoid VH was not significantly associated with worse OS (pooled HR 1.15, 95% CI 0.70–1.87; z=0.55). The Cochrane Q-test (chi-square 0.06, p=0.972) and I^2 test (0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (supplementary fig. 3, *D*; https://www.jurology.com).

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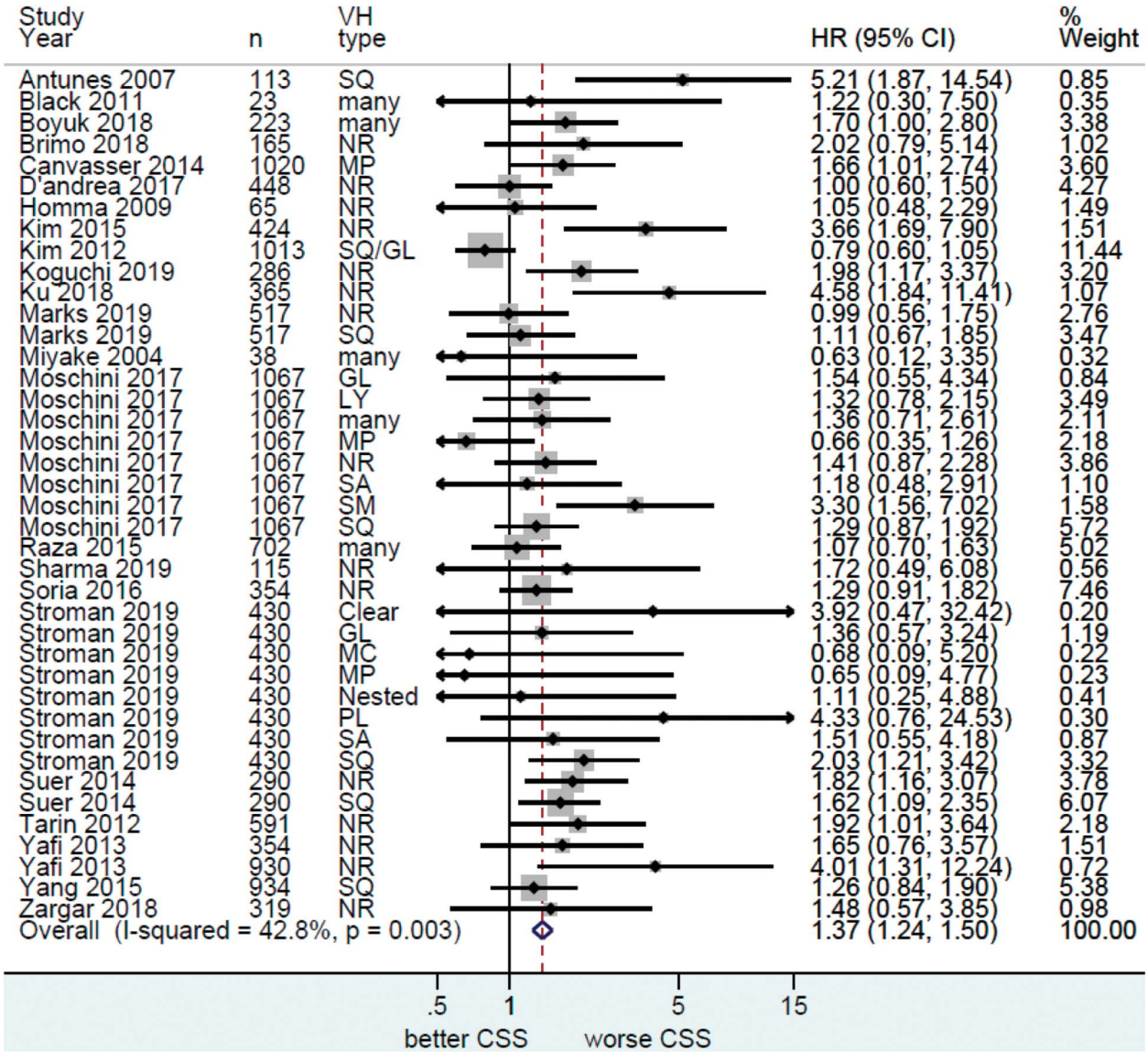

Figure 2. Forest plots show association of variant histology with cancer specific survival in urothelial carcinoma of bladder. *SQ*, squamous. *NR*, not reported. *MP*, micropapillary. *GL*, glandular. *LY*, lymphoepithelioma. *SA*, sarcomatoid. *SM*, small cell. *MC*, microcystic. *PL*, plasmacytoid.

Association of small cell VH with OS. Two studies including 1,472 patients provided data on the association of small cell VH with OS. The forest plot (fig. 6, *B*) indicated that small cell VH was significantly associated with worse OS (pooled HR 3.32, 95% CI 1.98–5.59; z=4.53). The Cochrane Q-test (chi-square 0.21, p=0.644) and I^2 test (0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (supplementary fig. 3, *E*; https://www.jurology.com).

Other VH associated with OS. Sarcoma and spindle VH types were significantly associated with worse OS in 1 study each. Nested and lymphoepithelioma VH types were found not to be significantly associated with worse OS in 1 study each.[15, 56, 61]

Sensitivity analysis. Sensitivity analyses were performed first through sequential deletion of any individual study to measure the effects of each study and second based on the quality of the studies included. Overall HRs were not significantly influenced by any individual study or by the quality of studies evaluated, suggesting the robustness and reliability of the results in our meta-analysis.

DISCUSSION

This meta-analysis investigated the prognostic value of VH in UCB. VH is usually associated with advanced stage, lymphovascular invasion and lymph node metastasis.[11,17] Additionally UCB with VH is more aggressive in appearance and has a

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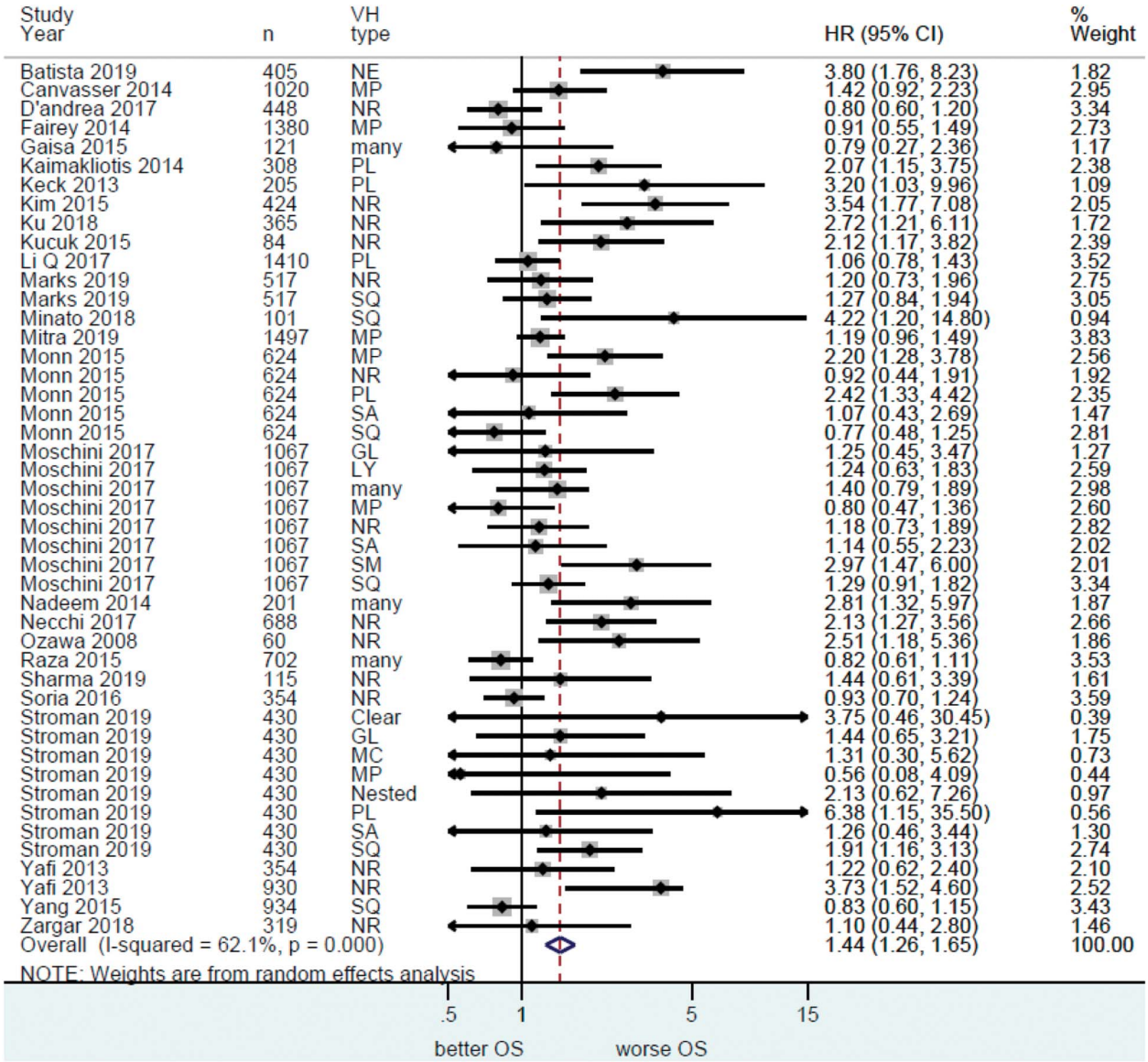

Figure 3. Forest plots demonstrate association of variant histology with overall survival in urothelial carcinoma of bladder. *NE*, neuroendocrine. *MP*, micropapillary. *NR*, not reported. *PL*, plasmacytoid. *SQ*, squamous. *SA*, sarcomatoid. *GL*, glandular. *LY*, lymphoepithelioma. *SM*, small cell. *MC*, microcystic.

worse prognosis than PUCB.[11,14,17] UC presents with different types of VH,[67] which are dissimilar in their biological, clinical and prognostic impact. We found that micropapillary, plasmacytoid and small cell VH subgroups were significantly associated with worse OS. While few studies have assessed these subgroups, it appears that VH could be used to select patients who might benefit from more intensive treatment such as adjuvant therapy. Moreover, these results suggest that UCB with VH requires a strict surveillance protocol.

Micropapillary VH

The micropapillary variant, characterized by small nests and aggregates of tumor cells in lacunae without vascular cores,[17,68] is associated with advanced clinicopathological features and an unfavorable prognosis. It has a prevalence of approximately 0.6% to 2.0% of all bladder carcinoma cases.[17,69-71] However, the molecular findings cannot account for the aggressive behavior of micropapillary disease.

While conventional UCs are categorized into basal, luminal and p53-like subtypes, a recent study on gene expression signatures showed that micropapillary tumors were predominantly of the luminal type.[69,72] Of conventional UCs the luminal subtype is typically associated with longer survival and less aggressive disease. However, downregulation of miR-296 and upregulation of its target genes,

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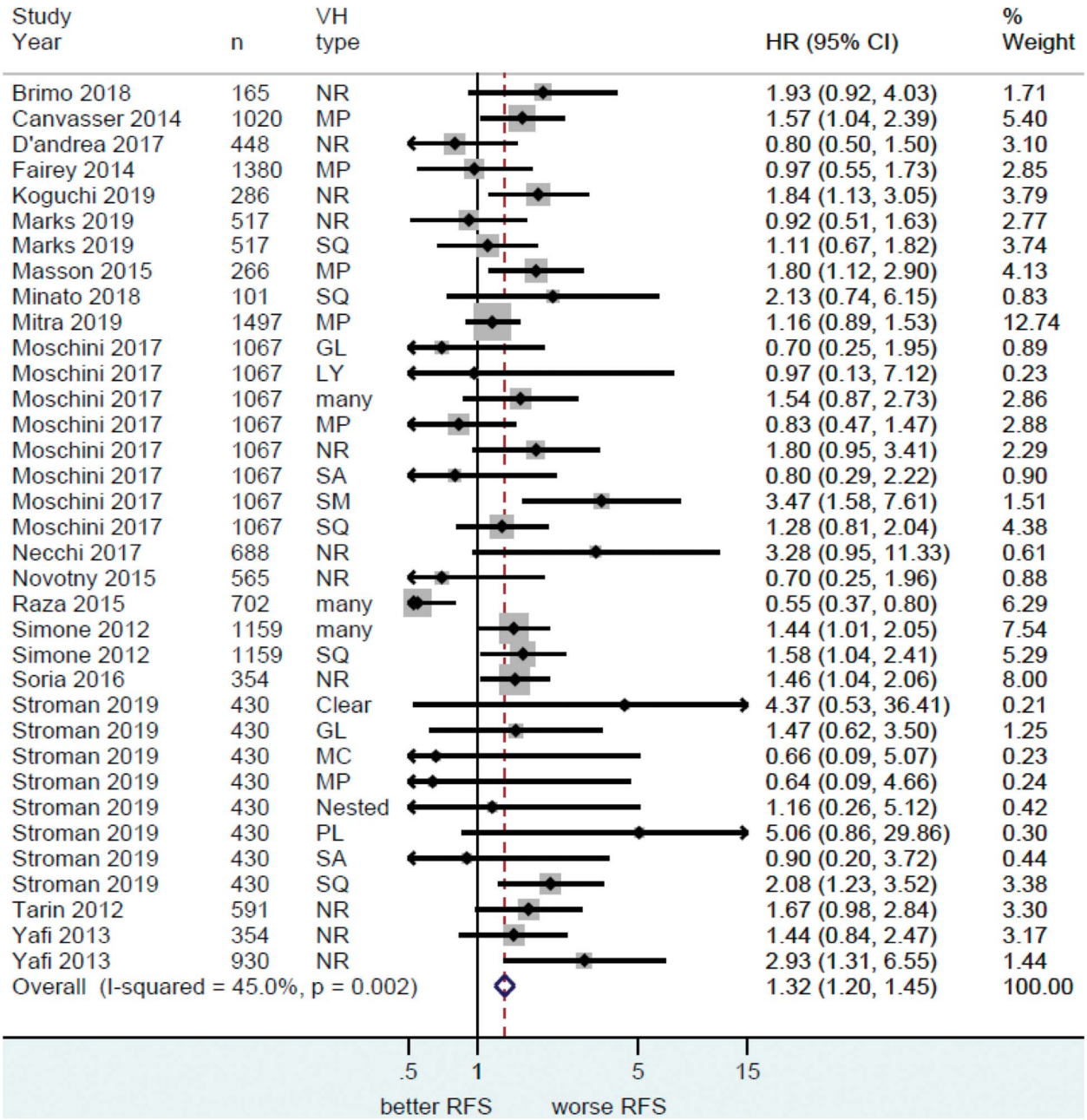

Figure 4. Forest plots reveal association of variant histology with recurrence-free survival in urothelial carcinoma of bladder. *NR,* not reported. *MP,* micropapillary. *SQ,* squamous. *GL,* glandular. *LY,* lymphoepithelioma. *SA,* sarcomatoid. *SM,* small cell. *PL,* plasmacytoid.

including activation of the RUVBL1 pathway, drives the expression signature of micropapillary disease. These differences may therefore account for a more aggressive disease course than conventional luminal UCs. Furthermore, a subset of micropapillary disease has features of the p53-like subtype, which is associated with chemotherapy resistance in conventional UCs and is the most aggressive of all conventional and micropapillary UCs. Thus, molecular differences might exist within the micropapillary UC group, depending on the presence of the p53-like subtype, which may lead to divergent outcomes with AC.

Squamous VH

The squamous variant is the most common of all VH subtypes, with an estimated incidence of up to 20% to 40% of cases.[73,74] Squamous VH appears bulky and polypoid, with solid necrotic masses often filling the bladder lumen, and is defined by the presence of intracellular bridges or keratinization.[13,75] Recently caveolin-1 demonstrated higher expression rates in squamous bladder cancer vs conventional bladder cancer (82% vs 43%, p <0.001). However, given the overexpression of this protein in benign squamous metaplasia,[76] it remains unclear whether caveolin-1

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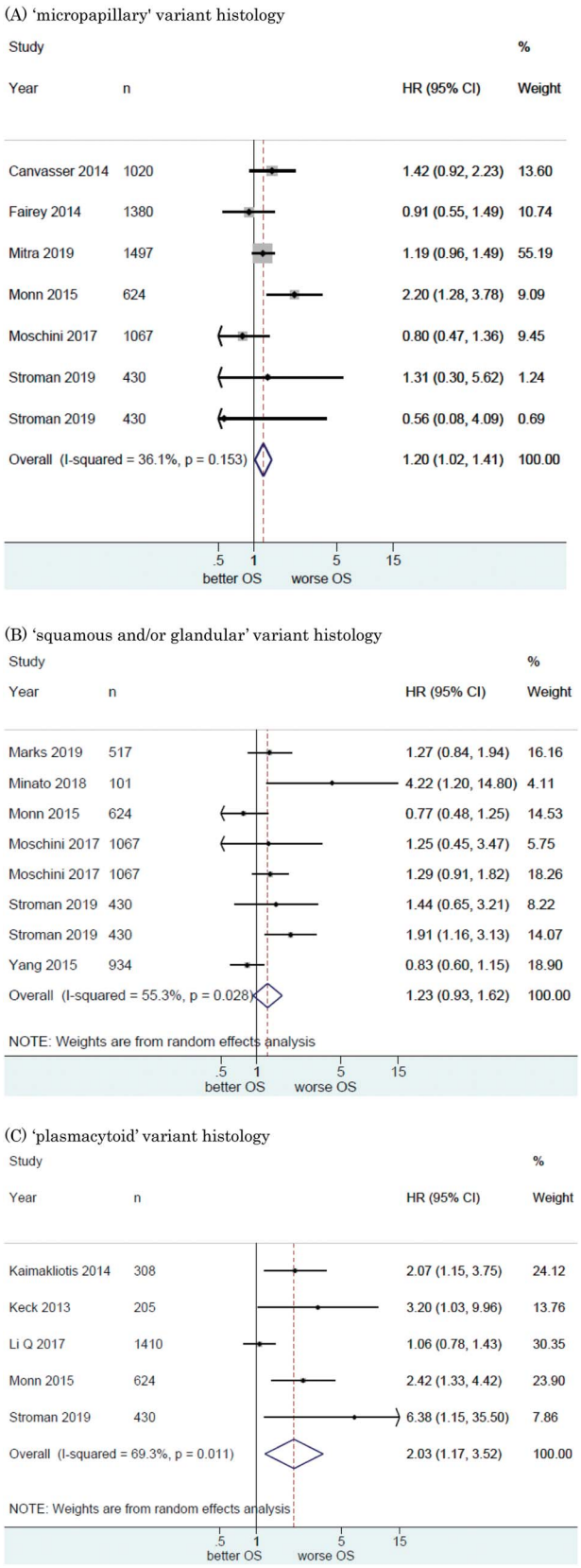

Figure 5. Forest plots show association of variant histology subgroups with overall survival. *A,* micropapillary variant histology. *B,* squamous and/or glandular variant histology. *C,* plasmacytoid variant histology.

has a role in early cell transformation and tumorigenesis. The glandular variant is the second most common of all VHs and may be found in up to 18% of all invasive tumors.[73,74] However, optimal management of the squamous and glandular variants remains controversial as they might coexist with other VH subtypes, such as micropapillary and sarcomatoid.

Plasmacytoid VH

Plasmacytoid is a rare and aggressive variant of UCB characterized by the presence of discohesive, individual cells with eccentrically located nuclei resembling plasma cells, as well as cells with intracytoplasmic vacuoles showing signet ring appearance.[77–79] It is characterized by aggressive clinicopathological features and frequent occurrence of peritoneal carcinomatosis, despite the apparent initial response to chemotherapy.[80,81] Whole exome and targeted sequencing performed on plasmacytoid carcinomas has revealed frequent somatic alterations in the CDH1 gene, which encodes for E-cadherin. This finding is notably specific for the plasmacytoid variant, with no CDH1 truncating mutations identified in the TCGA (The Cancer Genome Atlas) urothelial carcinoma cohort. The loss of E-cadherin (found in approximately 70% of plasmacytoid carcinomas but in only 11% of conventional urothelial carcinomas)[77] results in enhanced tumor cell migration and might explain the tendency of these tumors to recur locally with peritoneal metastases, accounting for an aggressive clinical course.

Small Cell VH

The small cell variant is morphologically identical to that in other organs but may have a classic urothelial component.[82] This rare tumor is composed of nests of small, round, malignant cells with pyknotic round to oval nuclei containing evenly dispersed "salt and pepper chromatin."[83] Systemic chemotherapy is essential to treat patients with a small cell variant. In studies of patients deemed unfit for or not receiving chemotherapy survival outcomes were poor, with median survival times of 3 to 5 months, even in patients with localized disease undergoing surgical treatment, compared to 15 to 33 months in those receiving local treatment and systemic chemotherapy.[84–86] Therefore, given the limited survival results with extirpative surgery alone, patients with this VH should be treated with multimodal therapy including systemic chemotherapy followed by local consolidating therapy such as RC and/or radiotherapy.

Management of VH

Optimal management of VH is controversial as current recommendations are based on retrospective

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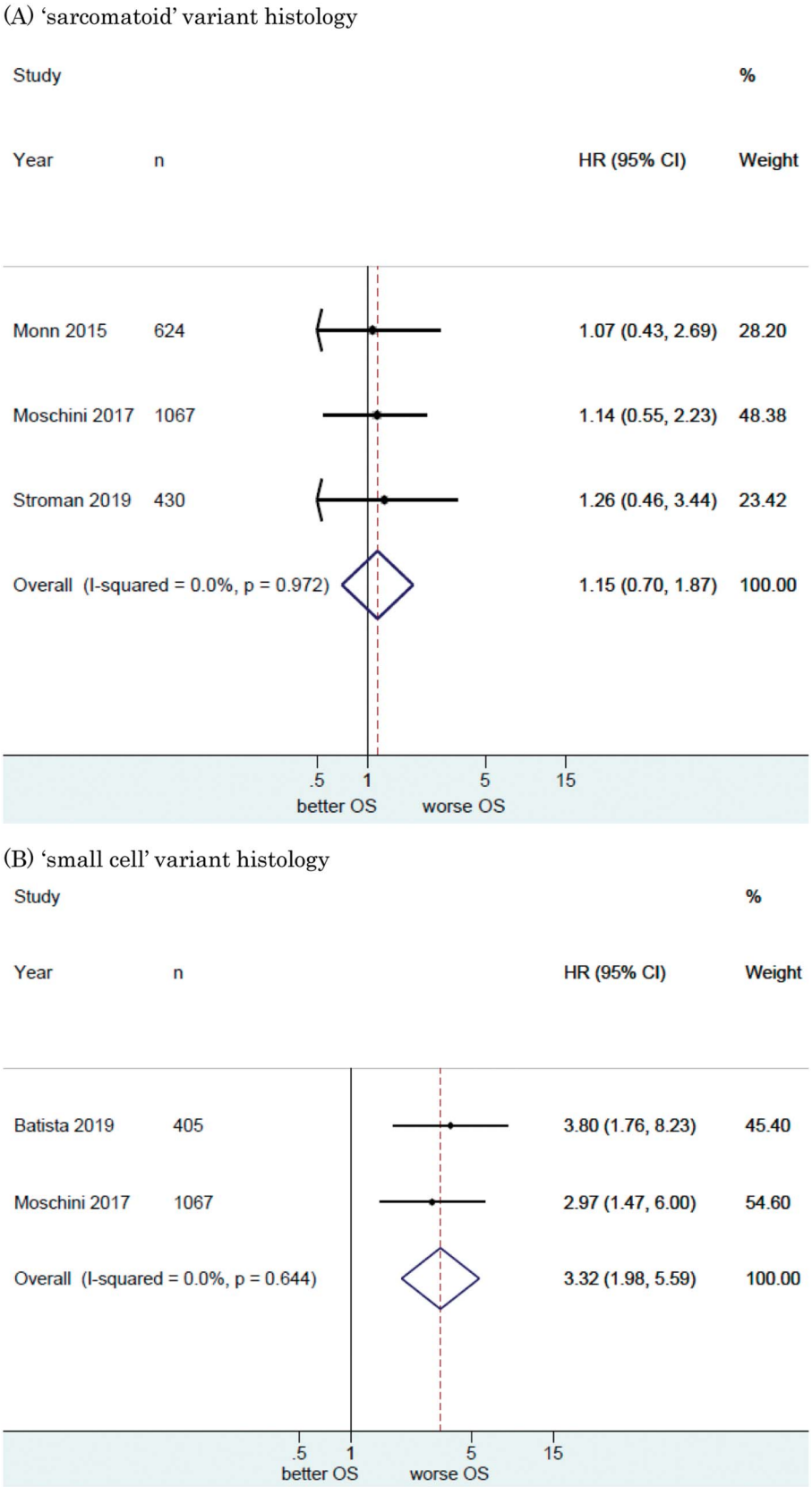

Figure 6. Forest plots demonstrate association of variant histology subgroups with overall survival. *A*, sarcomatoid variant histology. *B*, small cell variant histology.

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studies and extrapolation of data from PUCB. The survival benefit of cisplatin based chemotherapy is debatable, although current evidence does not preclude its use. Currently neoadjuvant chemotherapy and radical cystectomy with PLND are the mainstay of treatment for most cases of VH.

Chemosensitivity varies widely among the VH types. For example chemotherapy is deemed essential in patients with small cell and lymphoepithelioma-like VH.[87–89] Based on data from NCDB (National Cancer Database), Vetterlein et al reported that patients with neuroendocrine tumors benefit from NAC as evidenced by better OS and lower rates of nonorgan confined disease at the time of RC.[90] For other VH NAC also decreases the frequency of nonorgan confined disease. However, it has not translated into a significant OS benefit. In a study of 15,397 patients with bladder cancer treated with radical cystectomy using data from the NCDB Berg et al found no survival benefit for AC in patients with urothelial carcinoma with VH or pure VH.[91]

Accordingly other adjuvant treatment modalities must be considered after RC in patients with UCB with VH. However, a meta-analysis of OS indicated a higher hazard ratio for patients without NAC (1.93, 95% CI 1.27–2.93) compared to all patients. Therefore, while nonuse of NAC in the 7 studies may have adversely affected prognosis, patients with a poor prognosis (such as those with small cell VH) and the large proportion of patients with advanced disease included in these studies may have contributed to this result, making it difficult to evaluate the impact of NAC based on subanalyses.

In addition, among the included studies there were very few evaluating AC, which made it difficult to assess the impact of AC in this meta-analysis. Salvage chemotherapy is the cornerstone of treatment for small cell VH because of its high chemosensitivity.[88,89] On the other hand, squamous VH is generally associated with a poor response to chemotherapy.[92] No consensus has been reached regarding optimal treatment for micropapillary VH.[93] Furthermore, apparent lack of benefit from chemotherapy on OS has been confirmed in patients with sarcomatoid VH.[94] Moreover, recent data suggest that cisplatin based chemotherapy confers no survival benefit for patients with plasmacytoid VH, which early studies indicated was chemosensitive.[80,93,95]

It is important to evaluate the immune checkpoint inhibitor for its effect on VH in patients with UCB. Miller et al reported no significant association between VH subtypes and objective response rates among patients treated with immune checkpoint inhibitor.[96] Progression-free and overall survival are comparable between PUCB and VH, suggesting that histology subtypes may not be a biomarker of response to immune checkpoint inhibitor. Recently results of the PURE-01 (Pembrolizumab as Neoadjuvant Therapy before Radical Cystectomy in Patients with Muscle-Invasive Urothelial Bladder Carcinoma) study suggested a role for neoadjuvant pembrolizumab in patients with predominant VH, with those harboring squamous cell carcinoma or a lymphoepithelioma-like variant feature exhibiting major, albeit preliminary, pathological responses compared to those with other predominant VHs.[97] However, to date the effect of systemic therapy on VH remains to be fully examined.

Study Limitations

Our study has several limitations. There may be reporting bias because multiple series with negative results may be unpublished. Furthermore, all studies included in this meta-analysis were retrospective and might show selection bias. Most depended on database entries and might have suffered from a lack of secondary pathology reviews. Increasing focus in recent years on VH because of in-depth histopathological reviews conducted by fellowship trained genitourinary pathologists at academic centers might introduce an implicit selection bias. Indeed, VH was reported in only 14.0% of all patients from the 39 studies, in contrast to up to 30% of patients at final pathological examination following RC in recent years, and this large discrepancy was considered to reflect this bias.[11,13] While analysis of included studies indicated that VH varied widely in incidence between 2.2% and 45.2%, likely reflecting the pathological assessments that varied in quality between the institutions, appropriate VH assessment appears to be extremely important in the evaluation of patient prognosis with VH.

In addition, heterogeneity was detected in the OS analysis, limiting the value of these results. While RC was consistently used as the intervention of interest, no restriction had been imposed in this study on disease stage, extent of PLND or implementation of NAC/AC in selecting the population of interest, which contributed to the large heterogeneity of the population of interest. Particularly it was suggested that the analyses conducted without regard to their particular VH type, as well as the pathological evaluations that varied between the studies, may have contributed in large measure to significant heterogeneity in this meta-analysis. Although the random effects model takes into account heterogeneity, conclusions should be interpreted with caution.

Furthermore, the included studies allowed each VH type to be assessed only for OS but not for CSS given the paucity of data available for CSS. In

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addition, some studies included for analysis did not contain followup data or contained followup of less than 2 years, which is insufficient to draw conclusions regarding survival outcomes. Also, considering that not all VH types of bladder cancer behave similarly, it may be an oversimplification to compare all of these VHs for prognosis. Moreover, while this meta-analysis included only those studies that had performed multivariate analyses to provide HRs, some of these studies had not had their outcomes consistently or adequately adjusted for relevant prognostic determinants. Finally, pathological specimens were evaluated at each institution without secondary review, resulting in a potential bias in identification and reporting of VH. In addition, many studies failed to assess the proportion of VH in the specimens obtained, which may have affected the survival outcomes. These factors may result in suboptimal pathological reports with variable effects on the oncologic outcomes.

Few studies have evaluated the impact of the extent of VH. Compérat et al have highlighted that any amount of micropapillary VH is clinically significant, as the proportion of transurethral resection of bladder tumor specimen is associated with CSS.[98] Moreover, Moschini et al reported that the presence of a pure variant but not a mixed variant with UC is related to a detrimental effect on survival outcomes after RC.[99] In contrast, a single center study by Wang et al detected no differences in 3-year CSS between micropapillary variant percentage categories (10%, 10% to 50%, and more than 50%).[100] Another study with UC plus squamous and/or glandular VH by Kim et al indicated no CSS difference between variant percentage categories (less than vs greater than 30%).[41] To date, few studies have evaluated the impact of the extent of VH present, which might impact prognosis in affected individuals while the study results remain inconclusive. Therefore, future studies must address not only percentage presence but also types of VH in a comprehensive manner.

Nevertheless, the current meta-analysis suggests that VH might have true prognostic value in UCB. This could help improve the accuracy of postoperative nomograms and decision tools regarding followup strategies and, more importantly, adjuvant therapies.[7,101] Well designed prospective studies with long-term followup are needed to not only validate our findings, but also to determine whether incorporation of VH will improve current tools for risk stratification.

CONCLUSIONS

We found that VH was associated with increased risk of overall mortality, cancer specific mortality and disease recurrence in patients with UCB. Furthermore, VH independently predicted worse OS in patients with micropapillary, plasmacytoid and small cell VH subtypes, suggesting that VH is a crucial factor that should be incorporated into prognostic tools for patient counseling and treatment planning.

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