Prognostic value of preoperative hematologic biomarkers in urothelial carcinoma of the bladder treated with radical cystectomy: a systematic review and meta-analysis

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Abstract
This systematic review and meta-analysis aimed to assess the prognostic value of preoperative hematologic biomarkers in patients with urothelial carcinoma of the bladder treated with radical cystectomy. PUBMED, Web of Science, Cochrane Library, and Scopus databases were searched in September 2019 according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement. Studies were deemed eligible if they compared cancer-specific survival in patients with urothelial carcinoma of the bladder with and without pretreatment laboratory abnormalities. Formal meta-analyses were performed for this outcome. The systematic review identified 36 studies with 23,632 patients, of these, 32 studies with 22,224 patients were eligible for the meta-analysis. Several preoperative hematologic biomarkers were significantly associated with cancer-specific survival as follows: neutrophil – lymphocyte ratio (pooled hazard ratio [HR]: 1.20, 95% confidence interval [CI]: 1.11–1.29), hemoglobin (pooled HR: 0.87, 95% CI 0.82–0.94), C-reactive protein (pooled HR: 1.44, 95% CI 1.26–1.66), De Ritis ratio (pooled HR: 2.18, 95% CI 1.37–3.48), white blood cell count (pooled HR: 1.05, 95% CI 1.02–1.07), and albumin-globulin ratio (pooled HR: 0.26, 95% CI 0.14–0.48). Several pretreatment laboratory abnormalities in patients with urothelial carcinoma of the bladder were associated with cancer-specific mortality. Therefore, it might be useful to incorporate such hematologic biomarkers into prognostic tools for urothelial carcinoma of the bladder. However, given the study limitations including heterogeneity and retrospective nature of the primary data, the conclusions should be interpreted with caution.

Keywords Urothelial carcinoma of the bladder · Hematologic biomarker · Meta-analysis
Introduction

Urothelial carcinoma of the bladder (UCB) is the ninth most commonly diagnosed cancer worldwide [1]. Radical cystectomy (RC) with lymph node dissection is the mainstay treatment for very high-risk non-muscle-invasive and muscle-invasive UCB [2, 3]. Despite definitive therapy with curative intent, the 5-year overall survival of patients remains below 60% [4, 5]. Thus, various clinical and pathologic factors have been identified to assist in the risk stratification of UCB patients, thereby facilitating clinical decision-making regarding treatment intensification, follow-up and patient counselling [6, 7]. Currently, the majority of these factors are pathological features such as tumor stage, grade, lymph node status, concomitant carcinoma in situ, variant histology, surgical margin status, and lymphovascular invasion. Unfortunately, the accuracy of outcome prediction with these factors remains suboptimal, probably due to their failure to capture the full biologic potential of host-tumor interactions [8]. In addition, clinical, radiologic, and pre-RC pathologic factors have significant limitations, and do not allow for optimal clinical decision making [6, 9]. Therefore, there remains a need to identify other potential prognostic markers, in particular preoperatively, to improve the stratification of patients with muscle-invasive UCB.

Recently, there has been a surge of interest in the prognostic role of hematologic biomarkers in patients undergoing RC. Current research has suggested that hematologic biomarkers, such as neutrophil–lymphocyte ratio (NLR), C-reactive protein (CRP), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and hemoglobin (Hb), may have prognostic value in patients with UCB [3, 10]. However, the prognostic significance of hematologic biomarkers remains to be established in UCB treated with RC. Therefore, this systematic review and meta-analysis were conducted to summarize the available evidence as well as to determine whether preoperative hematologic biomarkers may help predict oncological outcomes in patients with UCB treated with RC. If such biomarkers are predictive of outcomes in this patient population, a panel of these markers could help identify and classify patients, as well as aid in the selection of patients for novel therapies that rely heavily on host-tumor interaction.

Methods

Search strategy

The systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11]. The PubMed, Web of Science, Cochrane Library, and Scopus databases were searched in September 2019 to identify reports on the prognostic value of blood-based biomarkers in UCB. The keywords used in our search strategy were: (cystectomy) AND (multivariate OR multivariable) AND (survival OR mortality): The primary outcome of interest was cancer-specific survival (CSS). Initial screening was performed independently by two investigators based on the titles and abstracts to identify ineligible reports, and reasons for exclusions were noted. Potentially relevant reports were subjected to a full-text review and the relevance of the reports was also confirmed after the data extraction process. Disagreements were resolved via consensus with the additional investigator.

Inclusion and exclusion criteria

Studies were included if they investigated patients treated for UCB with preoperative laboratory abnormalities (Patients) who had received radical cystectomy (Intervention) compared to those without preoperative laboratory abnormalities (Comparison) to assess the independent predictive value of blood-based biomarkers on CSS (Outcome) utilizing multivariate Cox regression analysis (Study design) in non-randomized observational, randomized, or cohort studies. We excluded reviews, letters, editorials, meeting abstracts, replies from authors, case reports and articles not published in English. In cases of duplicate publications, the higher quality or the most recent publication was selected. References of included manuscripts were further scanned for additional studies of interest.

Data extraction

Two investigators independently extracted the following information from the included articles: first author’s name, publication year, recruitment country, period of patient recruitment, number of patients, age, sex, study design, disease stage, oncological outcome, follow-up duration, pathological T stage, adjuvant chemotherapy, neoadjuvant chemotherapy, conclusion, and type of biomarkers. Subsequently, the hazard ratios (HR) and 95% confidence intervals (CI) of blood-based biomarkers associated with each of the outcomes were retrieved. The HRs were extracted from the multivariate analyses and all discrepancies regarding data extraction were resolved by consensus with the additional investigator.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies in accordance with the Cochrane Handbook for systematic reviews of interventions.
for included non-randomized studies [12, 13]. The scale rates following three factors: Selection (1–4 points), Comparability (1–2 points) and Exposure (1–3 points), with total scores ranging from 0 (lowest) to 9 (highest). The main confounders were identified as the important prognostic factors of CSS. The presence of confounders was determined by consensus and review of the literature. Studies with scores of more than 6 were identified as “high-quality” choices.

Statistical analyses

Forest plots were used to assess the multivariate HRs and summarize them to describe the relationships between blood-based biomarkers and CSS. Studies were not considered in the meta-analysis if they used Kaplan–Meier log-rank, univariate Cox proportional hazard regression, or general logistic regression analyses. In studies with only HRs and P-values, we calculated the corresponding 95% CIs [14, 15]. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated by using Cochrane’s $Q$ test and the $I^2$ statistic. Significant heterogeneity was indicated by a $P < 0.05$ in Cochrane’s $Q$ tests and a ratio > 50% in $I^2$ statistics. We used fixed-effects models for the calculation of pooled HRs for non-heterogeneous results [16–18]. Publication bias was assessed using funnel plots. All statistical analyses were performed using Stata/MP 14.2 (Stata Corp., College Station, TX); statistical significance level was set at $P < 0.05$.

Results

Study selection and characteristics

Our initial search identified 4861 records, and after removing of duplicates, 4192 remained (Fig. 1). A total of 4112 articles were excluded after screening the titles and abstracts, and a full-text review was performed for 80 articles. After applying the selection criteria, we identified 36 articles with 23,632 patients for the systematic review, of which, 32 articles with 22,224 patients were used for the meta-analysis [10, 19–53]. The extracted data from the 36 studies are outlined in Tables 1 and 2. All included studies had a retrospective design and were published between 2002 and 2019.
Table 1 Study characteristics

| Author   | Year | Region | Period       | N   | D   | Type of markers evaluated (cut off values)                                                                 | Significant markers                                      | NOS |
|----------|------|--------|--------------|-----|-----|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----|
| Buisan   | 2016 | Spain  | 2007–2015    | 75  | R   | NLR (continuous)                                                                                         | NLR                                                      | 7   |
| Calvete  | 2019 | Spain  | 2000–2015    | 121 | R   | Hb (13 g/dL)                                                                                            | Hb                                                       | 7   |
| Chipollini|2016 | USA    | 2008–2015    | 1026|R   | Hb (NR)                                                                                                 | Hb                                                       | 7   |
| D’Andrea  | 2017 | International | 1990–2012 | 4198|R   | LMR (3.5), NLR (2.7)                                                                                     | LMR, NLR                                                  | 7   |
| Ergani   | 2015 | Turkey | 2009–2014    | 148 | R   | Hb (12.2 g/dL)                                                                                          | Hb                                                       | 6   |
| Gershman | 2016 | USA    | 1980–2008    | 2086|R   | Hb (continuous)                                                                                         | Hb                                                       | 7   |
| Gierth   | 2015 | Germany | 2001–2011   | 684 | R   | Hb (male 13 g/dL, female 12 g/dL)                                                                        | Hb                                                       | 7   |
| Gondo    | 2012 | Japan  | 2000–2009    | 189 | R   | Hb (11.5 g/dL), NLR (2.5), Pt (300,000/uL), LDH (360u/L), CRP (0.5 mg/dL), Neu (6500/uL), Lym (1500/uL) | Hb, NLR                                                  | 7   |
| Gorgel   | 2017 | Turkey | 2006–2016    | 153 | R   | De Ritis (1.3)                                                                                          | De Ritis                                                 | 6   |
| Grimm    | 2015 | Germany | 2004–2013   | 664 | R   | CRP (0.5 mg/dl), Hb (13.4 g/dl)                                                                          | CRP, Hb                                                   | 7   |
| Ha       | 2019 | Korea  | 2008–2013    | 118 | R   | De Ritis (1.3)                                                                                          | De Ritis                                                 | 7   |
| Hermanns | 2014 | Canada | 1992–2012    | 424 | R   | Hb (continuous), NLR (3), Pt (continuous)                                                                | Hb, NLR, Pt                                              | 7   |
| Jo       | 2016 | Korea  | 2003–2014    | 200 | R   | Hb (male 13 g/dL, female 12 g/dL)                                                                        | Hb                                                       | 7   |
| Jokisch  | 2019 | Germany | 2004–2017   | 866 | R   | Pt (400,000/uL)                                                                                         | Pt                                                       | 7   |
| Kang     | 2017 | Korea  | 1999–2012    | 385 | R   | NLR (2.5)                                                                                               | NLR                                                      | 6   |
| Kluth    | 2015 | International | 1979–2012 | 967 | R   | Alb (continuous), Hb (continuous), LDH (continuous), Pt (continuous), WBC (continuous)                  | Alb, Hb, LDH, Pt, WBC                                     | 6   |
| Ku       | 2015 | Korea  | 1999–2011    | 419 | R   | Alb (3.5 g/dL), Lym (1000/uL), Pt (400,000/uL), CRP (10 mg/dL), WBC (11,000/uL), Neu (7500/uL)         | Alb, Lym, Pt                                              | 7   |
| Kwon     | 2014 | Korea  | 1990–2012    | 714 | R   | Alb (3.5 g/dL)                                                                                          | Alb                                                      | 7   |
| Lambert  | 2013 | USA    | 2004–2011    | 187 | R   | Alb (3.5 g/dL)                                                                                          | Alb                                                      | 7   |
| Liu J    | 2016 | China  | 2000–2013    | 296 | R   | AGR (1.6), Alb (continuous), Hb (continuous), Neu (continuous), Pt (continuous), WBC (continuous)       | AGR, Alb, Hb, Neu, Pt, WBC                                | 7   |
| Liu Z    | 2017 | China  | 2009–2013    | 189 | R   | AGR (1.55)                                                                                                | AGR                                                      | 7   |
| Lucca    | 2016 | International | 1979–2012 | 4061|R   | NLR (2.7)                                                                                               | NLR                                                      | 7   |
| Matsumoto| 2017 | Japan  | 1990–2013    | 594 | R   | eGFR (60 mL/min/1.73m²)                                                                                   | eGFR                                                     | 7   |
| Miyake   | 2017 | Japan  | 2006–2016    | 117 | R   | NLR (2.6), PLR (150), MLR (0.3)                                                                           | NLR, PLR                                                 | 6   |
| Moschini | 2014 | Italy  | 1995–2012    | 906 | R   | Hb (12 g/dL), Leukocyte (1000/uL), Pt (400,000/uL)                                                        | Hb, Leukocyte, Pt                                         | 7   |
| Ozcan    | 2015 | Turkey | 1990–2013    | 286 | R   | Leukocyte (11,000/uL), NLR (2.5), Neu (7700/uL), Lym (1500/uL)                                          | Leukocyte, NLR, Neu, Lym                                  | 7   |
| Rajwa    | 2018 | Poland | 2003–2015    | 144 | R   | LMR (continuous), NLR (continuous), PLR (continuous)                                                     | LMR, NLR, PLR                                             | 6   |
| Schubert | 2015 | Germany | 1999–2009   | 246 | R   | Hb (12 g/dL)                                                                                            | Hb                                                       | 7   |
| Sejima   | 2013 | Japan  | 2003–2011    | 249 | R   | Alb (continuous), CRP (continuous), Hb (continuous), LDH (continuous)                                   | Alb, CRP, Hb                                             | 7   |
| Tan      | 2017 | Singapore | 2002–2012   | 84  | R   | NLR (2.7), Hb (male13.5 g/dL, female 12.5 g/dL)                                                         | NLR                                                      | 7   |
| Todenhofer|2012|Germany|1999–2010    | 258 | R   | PLT (450,000/uL), Hb (male14g/dL, female 12 g/dL)                                                       | PLT                                                      | 7   |
| Un       | 2018 | Turkey | 2002–2012    | 296 | R   | Hb (NR), NLR (2.7)                                                                                      | Hb, NLR                                                  | 7   |
| Viers    | 2014 | USA    | 1994–2005    | 899 | R   | NLR (continuous)                                                                                        | NLR                                                      | 7   |
| Yang     | 2002 | China  | 1987–1997    | 310 | R   | Alb (3 g/dL), ALP (100U/L), Cr (1.5 mg/dL), Hb (10 g/dL), Pt (100,000/uL), WBC (10,000/uL)            | Alb, ALP, Cr, Hb, Pt, WBC                                 | 7   |
| Yoshida  | 2016 | Japan  | 1995–2013    | 302 | R   | LMR (NR)                                                                                                | LMR                                                      | 7   |
| Yuk      | 2019 | Korea  | 1991–2015    | 771 | R   | De Ritis (1.1)                                                                                          | De Ritis                                                 | 7   |

AGR albumin-globulin ratio, Alb albumin, ALP alkaline phosphatase, Cr creatinine, CRP C-reactive protein, D design, eGFR estimate glomerular filtration rate, Hb hemoglobin, LDH lactate dehydrogenase, LMR lymphocyte-to-monocyte ratio, Lym lymphocyte, MLR monocyte-lymphocyte ratio, Neu neutocyte, NLR neutrophil–lymphocyte ratio, NOS Newcastle–Ottawa Scale, PLR platelet-lymphocyte ratio, Pt platelet, R retrospective, WBC white blood cell.

with 13 studies being from Europe, 5 from North America, 15 from Asia and 3 from international collaboration. The
median age and follow-up ranged from 60.7 to 72 years, and 14 to 132 months, respectively; 19,185 of the studied patients were male and 4447 were female. The studies had a median NOS score of 7 (6–7)0.2329.

**Table 2** Patient characteristics

| Author     | Sex (M; F) | Age | Follow up (month) | pT stage (≥3) | NAC | AC |
|------------|------------|-----|-------------------|---------------|-----|----|
| Buisan     | 69; 9      | NR  | 31                | 35 (46.7%)    | 75 (100%) | NR |
| Calvete    | 118; 3     | 68.1| 51.4              | 80 (66.1%)    | 0   | 31 (25.6%) |
| Chipollini | 776; 250   | 68.8| 27.5              | 408 (39.8%)   | 387 (37.7%) | 142 (13.8%) |
| D’Andrea   | 3362; 836  | 67  | 42.4              | 1853 (44.1%)  | 0   | 954 (22.7%) |
| Ergani     | 132; 16    | 65.7| 21.12             | 70 (47.3%)    | 7 (4.7%)  | NR |
| Gershan    | 1712; 374  | 68  | 132               | 678 (32.5%)   | 130 (6.2%) | 192 (9.2%) |
| Gierth     | 551; 134   | 70  | 50                | 307 (44.9%)   | 0   | NR |
| Gondo      | 158; 31    | 68.4| 25.1              | NR            | 0   | NR |
| Gorgel     | 139; 14    | 61.65| NR               | 85 (50.4%)    | NR  | NR |
| Grimm      | 511; 153   | 70  | 24                | NR            | NR  | NR |
| Ha         | 98; 20     | 69  | 34.1              | NR            | 21 (17.8%) | NR |
| Hermanns   | 325; 99    | 70.1| 58.4              | 194 (45.7%)   | 29 (6.8%) | 87 (20.5%) |
| Jo         | 176; 24    | 67  | 28.6              | NR            | 12 (6.0%)  | NR |
| Jokisch    | 663; 203   | 70  | 38                | 410 (47.3%)   | NR  | NR |
| Kang       | 333; 52    | 66  | NR                | 139 (36.1%)   | 0   | 96 (24.9%) |
| Kluth      | 747; 220   | 66  | 18                | 679 (70.2%)   | 0   | 279 (28.9%) |
| Ku         | 362; 57    | 65.1| 37.7              | 177 (42.2%)   | NR  | NR |
| Kwon       | 636; 78    | 62.4| 64.1              | 319 (44.7%)   | 0   | 164 (23.0%) |
| Lambert    | 153; 34    | 67.4| 26.2              | 84 (44.9%)    | 35 (18.7%) | NR |
| Liu J      | 250; 46    | 61.71| 72             | 102 (34.5%)   | 0   | 75 (25.3%) |
| Liu Z      | 164; 24    | NR  | 38                | 69 (36.5%)    | 0   | 33 (17.5%) |
| Lucca      | 3240; 821  | 66.1| 42                | 1912 (47.1%)  | 0   | 963 (23.7%) |
| Matsumoto  | 482; 112   | 67  | 48                | 251 (42.3%)   | 0   | 166 (27.9%) |
| Miyake     | 95; 22     | 72  | 22                | 43 (36.8%)    | 47 (40.2%) | 20 (17.1%) |
| Moschini   | 754; 152   | 68  | 41                | 393 (43.4%)   | 0   | NR |
| Ozcan      | 256; 30    | 60.7| 28                | 124 (43.3%)   | 0   | NR |
| Rajwa      | 115; 29    | NR  | 14                | NR            | 0   | NR |
| Schubert   | 191; 55    | NR  | 30                | 122 (49.6%)   | 0   | 40 (16.3%) |
| Sejima     | 214; 35    | 72  | 24.8              | 108 (43.4%)   | 0   | 16 (6.4%) |
| Tan        | 63; 21     | 67  | 30.1              | 43 (51.2%)    | 0   | NR |
| Todenhofer | 201; 57    | NR  | 30                | 129 (50.0%)   | 0   | 41 (15.9%) |
| Un         | 254; 42    | 65.7| 24.5              | 114 (38.5%)   | 0   | NR |
| Viers      | 723; 176   | 69  | 130.8             | 347 (38.6%)   | 0   | 117 (13.0%) |
| Yang       | 275; 35    | NR  | 71                | NR            | NR  | 242 (78.1%) |
| Yoshida    | 238; 64    | 70  | 81.6              | 134 (44.4%)   | 20 (6.6%) | 62 (20.55) |
| Yuk        | 652; 119   | 64.8| 84                | 255 (33.1%)   | 103 (13.4%) | 173 (22.4%) |

**AC** adjuvant chemotherapy, **F** female, **M** male, **NAC** neoadjuvant chemotherapy, **NR** not reported, **p** pathological

**Meta-analysis**

**Association of NLR with CSS in UCB**

Twelve studies including 11, 158 patients provided data on the association of NLR with CSS in UCB. The forest plot (Fig. 2a) revealed that NLR was significantly associated with CSS in UCB (pooled HR: 1.20, 95% CI 1.11–1.29; z = 4.83). The Cochrane’s Q test (Chi² = 56.41; P = 0.000) and I² test
Fig. 2 Forest plot (association of hematologic biomarkers with cancer-specific survival). a neutrophil–lymphocyte ratio; b hemoglobin; c platelet; d albumin; e lymphocyte-to-monocyte ratio; f de ritis ratio; g albumin-globulin ratio; h c-reactive protein; i platelet-lymphocyte ratio; j white blood cell; k leukocyte

(A) neutrophil–lymphocyte ratio

Table 2

| Study Year | n  | HR (95% CI) | % |
|------------|----|-------------|---|
| 2016       | 75 | 1.27 (1.11, 1.44) | 11.79 |
| 2015       | 199 | 1.20 (1.26, 1.40) | 15.63 |
| 2015       | 189 | 1.95 (1.83, 2.06) | 1.24 |
| 2015       | 424 | 1.88 (1.39, 2.50) | 4.00 |
| 2015       | 385 | 1.16 (1.06, 1.27) | 14.66 |
| 2015       | 4061 | 1.21 (1.07, 1.37) | 12.25 |
| 2015       | 117 | 1.50 (0.60, 3.70) | 6.02 |
| 2015       | 286 | 1.97 (1.48, 2.69) | 1.29 |
| 2015       | 144 | 1.05 (0.82, 1.35) | 18.43 |
| 2015       | 84 | 2.68 (1.19, 6.01) | 0.77 |
| 2015       | 296 | 2.61 (1.67, 3.43) | 0.64 |
| 2015       | 899 | 1.94 (1.01, 3.58) | 18.23 |

Overall (I² = 80.5%, p = 0.000)

NOTE: Weights are from random effects analysis

15
10
5
better CSS worse CSS

(B) hemoglobin

Table 3

| Study Year | n  | HR (95% CI) | % |
|------------|----|-------------|---|
| 2019       | 121 | 0.63 (0.38, 1.07) | 1.68 |
| 2017       | 1026 | 0.99 (0.70, 1.50) | 2.91 |
| 2015       | 148 | 0.35 (0.12, 0.96) | 0.44 |
| 2015       | 2086 | 0.91 (0.57, 1.44) | 17.20 |
| 2014       | 684 | 0.62 (0.46, 0.82) | 4.54 |
| 2012       | 189 | 0.27 (0.12, 0.59) | 0.76 |
| 2012       | 664 | 0.60 (0.40, 0.90) | 3.67 |
| 2011       | 424 | 0.96 (0.92, 0.99) | 17.86 |
| 2017       | 200 | 0.37 (0.11, 1.23) | 0.34 |
| 2015       | 372 | 0.88 (0.62, 1.24) | 15.97 |
| 2015       | 296 | 1.00 (0.99, 1.02) | 18.62 |
| 2014       | 906 | 0.48 (0.31, 0.74) | 2.32 |
| 2013       | 249 | 0.81 (0.67, 0.98) | 8.01 |
| 2018       | 296 | 1.07 (0.86, 1.33) | 6.74 |
| 2018       | 296 | 0.87 (0.62, 0.94) | 100.00 |

Overall (I² = 80.5%, p = 0.000)

NOTE: Weights are from random effects analysis

15
10
5
better CSS worse CSS

(C) platelet

Table 4

| Study Year | n  | HR (95% CI) | % |
|------------|----|-------------|---|
| 2014       | 424 | 1.19 (1.03, 1.37) | 2.55 |
| 2013       | 866 | 2.23 (1.51, 3.30) | 0.36 |
| 2015       | 372 | 0.94 (0.89, 1.08) | 5.22 |
| 2015       | 419 | 2.11 (1.02, 4.38) | 0.10 |
| 2015       | 296 | 1.00 (0.99, 1.00) | 47.83 |
| 2014       | 906 | 1.00 (0.99, 1.00) | 44.14 |
| 2014       | 906 | 1.01 (0.98, 1.03) | 100.00 |

Overall (I² = 81.0%, p = 0.000)

NOTE: Weights are from random effects analysis

15
10
5
better CSS worse CSS

Association of Hb with CSS in UCB

Fourteen studies including 7661 patients provided data on
(D) albumin

| Study     | Year | n   | HR (95% CI) | Weight |
|-----------|------|-----|-------------|--------|
| Kuh 2015  | 2015 | 372 | 0.84 (0.97, 1.07) | 15.51  |
| Ku 2015   | 2015 | 419 | 0.96 (0.93, 1.00) | 2.52   |
| Kwon 2014 | 2014 | 714 | 0.91 (0.85, 1.40) | 4.36   |
| Lanzieri  | 2013 | 187 | 0.64 (0.31, 1.31) | 2.46   |
| Liu J 2016| 2016 | 200 | 0.98 (0.88, 1.09) | 74.65  |
| Dajna 2013| 2013 | 246 | 1.09 (0.48, 2.56) | 1.13   |
| Overall   |      |     | 0.99 (0.86, 1.12) | 100.00 |

(E) lymphocyte-to-monocyte ratio

| Study     | Year | n   | HR (95% CI) | Weight |
|-----------|------|-----|-------------|--------|
| D’Andrea  | 2017 | 4198| 1.30 (1.20, 1.50) | 38.59  |
| Rajewa   | 2018 | 144 | 0.75 (0.64, 0.88) | 37.63  |
| Yoshida  | 2016 | 302 | 1.68 (0.93, 3.04) | 23.78  |
| Overall   |      |     | 1.12 (0.71, 1.78) | 100.00 |

NOTE: Weights are from random effects analysis

(F) de ritis ratio

| Study     | Year | n   | HR (95% CI) | Weight |
|-----------|------|-----|-------------|--------|
| Gogol 2017| 2017 | 153 | 5.79 (2.21, 15.13) | 16.53  |
| Hu 2019   | 2019 | 118 | 1.65 (1.24, 2.76) | 39.92  |
| Yik 2019  | 2019 | 771 | 1.76 (1.26, 2.48) | 43.55  |
| Overall   |      |     | 2.16 (1.37, 3.48) | 100.00 |

NOTE: Weights are from random effects analysis
Fig. 2 (continued)

(G) albumin-globulin ratio

| Year | n   | HR (95% CI) | Weight |
|------|-----|-------------|--------|
| Liu J 2018 | 296 | 0.39 (0.11, 0.88) | 67.72 |
| Liu 2 2017 | 189 | 0.20 (0.11, 0.38) | 62.39 |
| Overall (I-squared = 0.0%, p = 0.637) | | 0.39 (0.14, 0.64) | 100.00 |

(H) c-reactive protein

| Year | n   | HR (95% CI) | Weight |
|------|-----|-------------|--------|
| Grimm 2015 | 664 | 1.50 (1.10, 2.06) | 16.33 |
| Sejima 2013 | 249 | 1.43 (1.23, 1.67) | 83.87 |
| Overall (I-squared = 0.0%, p = 0.816) | | 1.44 (1.26, 1.66) | 100.00 |

(I) platelet-lymphocyte ratio

| Year | n   | HR (95% CI) | Weight |
|------|-----|-------------|--------|
| Miyake 2017 | 117 | 0.80 (0.30, 1.90) | 0.00 |
| Rajwa 2018 | 144 | 1.00 (1.00, 1.00) | 100.00 |
| Overall (I-squared = 0.0%, p = 0.635) | | 1.00 (1.00, 1.00) | 100.00 |
the association of Hb with CSS in UCB. The forest plot (Fig. 2b) revealed that Hb was significantly associated with CSS in UCB (pooled HR, 0.87; 95% CI, 0.82–0.94; \( z = 3.71 \)). The Cochrane’s \( Q \) test (Chi\(^2\) = 79.01; \( P = 0.000 \)) and \( I^2 \) test (\( I^2 = 83.5\% \)) revealed significant heterogeneity.
Fig. 3 Funnel plot (association of hematologic biomarkers with cancer-specific survival). a neutrophil–lymphocyte ratio; b hemoglobin; c platelet; d albumin; e lymphocyte-to-monocyte ratio; f de Ritis ratio; g albumin-globulin ratio; h C-reactive protein; i platelet-lymphocyte ratio; j white blood cell; k leukocyte

The funnel plot identified six studies over the pseudo-95% CI (Fig. 3b).
Association of platelet count with CSS in UCB

Six studies including 3,283 patients provided data on the association of platelet count (Plt) with CSS in UCB. The forest plot (Fig. 2c) revealed that Plt was not significantly associated with CSS in UCB (pooled HR: 1.01, 95% CI 0.98–1.03; z = 0.55). The Cochrane’s Q test (Chi² = 26.31; P = 0.000) and I² test (I² = 81.0%) revealed significant heterogeneity. The funnel plot identified three studies over the pseudo-95% CI (Fig. 3c).

Association of albumin with CSS in UCB

Six studies including 2,237 patients provided data on the association of albumin (Alb) with CSS in UCB. The forest plot (Fig. 2d) revealed that Alb was not significantly associated with CSS in UCB (pooled HR: 0.93, 95% CI 0.85–1.02; z = 1.45). The Cochrane’s Q test (Chi² = 5.80; P = 0.327) and I² test (I² = 13.7%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Fig. 3d).

Association of LMR with CSS in UCB

Three studies including 4,644 patients provided data on the association of LMR with CSS in UCB. The forest plot (Fig. 2e) revealed that LMR was not significantly associated with CSS in UCB (pooled HR: 1.12; 95% CI 0.71–1.78; z = 0.50). The Cochrane’s Q test (Chi² = 31.73; P = 0.000) and I² test (I² = 93.7%) revealed significant heterogeneity. The funnel plot identified two studies over the pseudo-95% CI (Fig. 3e).

Association of De Ritis ratio with CSS in UCB

Three studies including 1,042 patients provided data on the association of De Ritis ratio with CSS in UCB. The forest plot (Fig. 2f) revealed that De Ritis ratio was significantly associated with CSS in UCB (pooled HR: 2.18; 95% CI 1.37–3.48; z = 3.30). The Cochrane’s Q test (Chi² = 5.35; P = 0.069) and I² test (I² = 62.6%) revealed significant heterogeneity. The funnel plot identified one study over the pseudo-95% CI (Fig. 3f).

Association of Albumin-globulin ratio with CSS in UCB

Two studies including 485 patients provided data on the association of albumin-globulin ratio (AGR) with CSS in UCB. The forest plot (Fig. 2g) revealed that AGR was significantly associated with CSS in UCB (pooled HR: 0.26, 95% CI 0.14–0.48; z = 4.27). The Cochrane’s Q test (Chi² = 0.04; P = 0.837) and I² test (I² = 0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Fig. 3g).
Association of CRP with CSS in UCB

Two studies including 913 patients provided data on the association of CRP with CSS in UCB. The forest plot (Fig. 2h) revealed that CRP was significantly associated with CSS in UCB (pooled HR: 1.44, 95% CI 1.26–1.66; z = 5.15). The Cochrane’s Q test (Chi² = 0.05; P = 0.816) and I² test (I² = 0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Fig. 3i).

Association of Platelet-lymphocyte ratio with CSS in UCB

Two studies including 261 patients provided data on the association of platelet-lymphocyte ratio (PLR) with CSS in UCB. The forest plot (Fig. 2i) revealed that PLR was not significantly associated with CSS in UCB (pooled HR: 1.00, 95% CI 1.00–1.00; z = 0.01). The Cochrane’s Q test (Chi² = 0.22; P = 0.635) and I² test (I² = 0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Fig. 3j).

Association of White blood cell with CSS in UCB

Two studies including 668 patients provided data on the association of white blood cell (WBC) with CSS in UCB. The forest plot (Fig. 2j) revealed that WBC was significantly associated with CSS in UCB (pooled HR: 1.44, 95% CI 1.26–1.66; z = 5.15). The Cochrane’s Q test (Chi² = 0.05; P = 0.816) and I² test (I² = 0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Fig. 3k).

Association of leukocyte with CSS in UCB

Two studies including 1, 192 patients provided data on the association of leukocyte with CSS in UCB. The forest plot (Fig. 2k) revealed that leukocyte was not significantly associated with CSS in UCB (pooled HR: 1.24, 95% CI 0.51 – 3.04; z = 0.02). The Cochrane’s Q test (Chi² = 3.02; P = 0.097) and I² test (I² = 63.6%) revealed significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Fig. 3k).

Other factors associated with CSS (in one paper only)

Estimate glomerular filtration rate (eGFR), and lymphocyte were significantly associated with CSS in one study each. Lactate dehydrogenase (LDH), and neutrocyte were found not to be significantly associated with CSS in one study each.

Discussion

This systematic review and meta-analysis were conducted to investigate the prognostic value of preoperative hematologic biomarkers in UCB, based on their association with CSS. Study results indicate that high preoperative NLR, CRP, WBC, and De Ritis ratio, as well as low AGR, and Hb are significantly associated with worse CSS.

First, De Ritis ratio was found to be associated with CSS in UCB, potentially as a marker of cellular metabolism and cancer cell turnover. It is generally assumed that alanine aminotransferase (ALT) is more liver-specific, whereas aspartate aminotransferase (AST) is widely expressed in different tissue types [54]. Therefore, pathological conditions associated with tumor proliferation, tumor cell turnover, and tissue damage, are thought to be more likely to increase AST than ALT, thus making the AST/ALT ratio an attractive potential biomarker [55]. However, the exact mechanism underlying the correlation between elevated AST/ALT and poor prognosis in UCB patients remains to be elucidated. Most cancer cells rely on anaerobic glycolysis to generate the energy required for survival, growth and metastasis even in the presence of oxygen via a process referred to as the “Warburg effect” [56]. Furthermore, increased glycolysis has been shown to be linked to several alterations in mitochondrial activity involving NADH-related enzymes and glucose transporters, and high LDH and cytosolic NADH/NAD+ have been shown to be essential for the maintenance of this enhanced glycolysis [57, 58]. AST is known to form part of the malate-aspartate shuttle pathway facilitating NADH/NAD+ conversion [59]. Therefore, AST/ALT may be related to tumor metabolism in many glucose-utilizing malignancies, such as UC [60–62].

Second, AGR was found to be associated with CSS in UCB. Of the 2 major human serum proteins evaluated in AGR, albumin and globulin, albumin is generally used to assess nutritional status and severity of disease. Low albumin has been shown to reflect malnutrition, which is common among patients with cancer, leading to disruption of a number of human defense mechanisms, such as anatomic barriers, cellular and humoral immunity, and phagocyte function [63, 64]. Moreover, albumin is now considered a marker of inflammatory response in addition to a nutritional marker [65, 66]. Globulin (derived from total protein minus the albumin fraction) consists of various pro-inflammatory proteins, including CRP, complement components, and immunoglobulins, and is, therefore, a central component of immunity and inflammation. Chronic inflammation markers play an important role in the proliferation, progression, development, and metastasis of tumor cells. Thus, AGR, as a combination of 2 separate predictors of adverse outcome, may have greater predictive value, given that nutritional...
status and systemic inflammatory response are both implicated in the outcome of patients with UCB undergoing RC.

Third, as an index of hypoxia, Hb was found to be associated with CSS in UCB. Hypoxia, which is commonly seen in advanced tumors, represents an imbalance between oxygen supply and consumption and thus may contribute to the resistance of tumor cells to therapy, whose impact may also be further enhanced by anemia [67, 68]. Tumor hypoxia has been shown to induce expression of hypoxia-inducible factor 1α (HIF1α), which is known to be integral to adaptively responding to hypoxia by targeting many genes involved in facilitating tumor survival, proliferation, invasion, and metastasis [69–71]. Furthermore, research suggests that hypoxia may promote tumor progression by inducing genetic changes and clonal selection in tumor cells [72].

Finally, in addition to AGR, several markers of the systemic inflammatory response, such as CRP, WBC, and NLR were shown to be significantly associated with CSS in UCB. These markers are known to be stimulated by cancer-related inflammatory factors, such as interleukin-6 thus sensitively reflecting cancer-related inflammation [7, 73, 74]. Cancer and inflammation are linked through both extrinsic and intrinsic pathways, with the former being activated by infection or chronic inflammation, and the latter being driven by genetic changes, such as oncogene activation or tumor suppressor gene deactivation. Both pathways activate key transcription factors, primarily nuclear factor -kB, signal transducer and activator of transcription 3, and HIF1α in tumor cells, which in turn lead to inflammatory mediators and cyclooxygenase-2 being produced, resulting in cancer-related inflammation and further promotion of tumor progression [7]. Therefore, the elevation of these systemic inflammatory response biomarkers impacts cancer growth and development [75]. Moreover, not only above mentioned systemic inflammatory markers, anemia is also brought about by inflammation such as IL-6 [76]. Hypoxia due to anemia will lead to increased HIF1α, which then activate Glucose transporter 1 and Phosphofructokinase-2 involved in glycolysis, leading to an increase of De Ritis ratio [69, 77–79]. Thus, the hematomal biomarkers we identified are all related to inflammation.

Although this meta-analysis revealed a strong association between several biomarkers and UCB mortality, it has some limitations that need to be taken into account. First, reporting bias could have led to non-publication of negative results. All the studies included were retrospective in design, thus increasing the risk of selection bias. Second, unknown pre-treatment factors (e.g., nutritional deficiencies, comorbidities, medications, and lifestyle factors) may have affected the hematologic biomarkers, thus producing systematic bias. Third, there were no established cut-off values for hematologic biomarkers among the studies evaluated, with the cut-off value being chosen by most investigators based on statistical methods (e.g., based on the highest sensitivity and specificity), the lower or higher limit of normal, or with pre-defined biomarker cut-off values from the literature. Fourth, the preoperative chemotherapeutic protocols were heterogeneous between the studies included, which did not allow each individual protocol to be assessed for its impact on the prognostic factors evaluated. In particular, it was a major limitation of the study that the hematologic biomarkers were not readily evaluable for their prognostic value in patients receiving and those not receiving NAC. Fifth, this systematic review and meta-analysis included no patients receiving immunotherapy. In this era of immunotherapy and other newly available targeted therapies, it remains unclear how the results of this meta-analysis may direct impact on patient management. Sixth, while it is crucial to examine hematologic biomarkers for their combined prognostic significance in UCB, this has not been adequately addressed in this systematic review and meta-analysis. It is a further limitation of the study that it was confined to the analysis of preoperative biomarkers, to the exclusion of relevant perioperative biomarkers. Seventh, despite its relevance, intravesical therapy prior to RC was not readily evaluable for its prognostic significance in UCB due to the paucity of data available from the literature. Finally, heterogeneity was detected in the CSS analysis, thus limiting the value of these results. Although the random effect model was used to address heterogeneity among the studies evaluated, the conclusions should be interpreted with caution. Therefore, well-designed prospective studies with long-term follow-up are required to validate the prognostic value of biomarkers in this setting, and to determine whether they could improve the current tools for risk stratification of patients with UCB.

Conclusions

This meta-analysis revealed that several preoperative hematologic biomarkers were associated with an increased risk of cancer-specific mortality in patients with UCB. Therefore, it might be useful to incorporate such hematologic biomarkers into prognostic tools to help with appropriate risk stratification of patients with UCB. In addition, low AGR had the highest HR, suggesting indirectly potentially stronger prognostic value than any other biomarkers.

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Compliance with ethical standards

Conflict of interest  None of the authors have conflicts of interest to disclose.

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