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Prognostic blood-based biomarkers in patients treated with neoadjuvant chemotherapy for urothelial carcinoma of the bladder: A systematic review

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Abstract

Purpose: The present systematic review aimed to identify prognostic values of blood-based biomarkers in patients treated with neoadjuvant chemotherapy (NAC) for urothelial carcinoma of the bladder (UCB).

Material and Methods: The PubMed, Web of Science, and Scopus databases were searched in August 2020 according to the PRISMA statement. Studies were deemed eligible if they compared oncological outcomes in patients treated with NAC for UCB with and without pretreatment laboratory abnormalities.

Results: Overall, ten studies, including 966 patients who underwent NAC, met our eligibility criteria. Six studies provided data on pretreatment neutrophil to lymphocyte ratio (NLR) with contradicting results on its association with pathologic response (PR) and complete pathologic response (pCR); some studies reported a strong association between a high level of pretreatment NLR and worse survival outcomes. Two studies reported that higher pretreatment platelet-lymphocyte ratio (PLR) is associated with a lower likelihood of achieving PR and/or pCR, while lymphocyte count alone had the opposite association. One study reported a negative association between pretreatment

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blood-based myeloid-derived suppressors cells and pCR. Patients who experienced a remission have been reported to have higher level of lymphocyte subsets (CD3+, CD4+, CD57+ cells, the ratio of CD4+/CD8+) compared to those who had progression. One study found that low pretreatment blood-based human chorionic gonadotrophin b subunit (hCGβ) was associated with improved overall survival (OS). High levels of epithelial tumor markers (CA-125, CA 19-9) were also associated with worse OS and recurrence-free survival in the NAC setting.

Conclusion: Current evidence suggests that several readily available, easy measurable blood-based biomarkers hold promise to improve our selection of UCB patients who are likely benefit from NAC. However, their role as an adjunct to established histopathologic characteristics for clinical decision-making requires further validation along the biomarker phased approach.

Keywords: Biomarkers; UCB; Bladder cancer; Neoadjuvant chemotherapy; NAC; Systematic review

1. Introduction

Urothelial carcinoma of the bladder (UCB) is the sixth most commonly diagnosed cancer [1,2]. Current guidelines recommend cisplatin-based neoadjuvant chemotherapy (NAC) prior to radical cystectomy as the preferred treatment of muscle-invasive UCB in cisplatin-fit patients [3,4]. However, a significant proportion of patients receiving NAC do not benefit clinically, resulting in a risk of overtreatment and exposure to unnecessary adverse events. [5]. Moreover, NAC has its limitations leading to moderate uptake in the community [6−8]. Accurate identification of patients who are most likely to benefit from NAC is of paramount importance in order to improve patient survival, while preventing unnecessary adverse events specifically in the age of novel therapeutics such as checkpoint immunotherapy [9,10]. Nowadays, despite the number of publications on potential markers and models associated with NAC response in UCB patients, none is validated or widely used in the clinical practice [11,12].

Systemic inflammation plays an important role in cancer development and progression and has been comprehensively studied in UCB [13,14]. Serum inflammatory biomarkers, especially the neutrophil to lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), have been studied as potential predictors of response to NAC in UCB [15−17]. More generally, blood-based biomarkers are promising tools as they are cost-effective, widely available, and repeatable. However, the use of pretreatment blood-based biomarkers as predictors of clinical outcomes in patients treated with NAC for UCB are still poorly studied along the phased biomarker validation paradigm [18−20].

Therefore, the aim of this systematic review was to summarize the available evidences and determine whether pretreatment blood-based biomarkers may help predict oncological outcomes in patients treated with NAC for UCB. This review could serve as a benchmark for further developments

2. Material and methods

2.1. Literature search

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [21]. This study's protocol was registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO; Registration ID CRD42020208413).

The PubMed, Web of Science, and Scopus databases were searched in August 2020 to identify studies reporting on the prognostic value of blood-based biomarkers in patients treated with NAC for UCB. A comprehensive systematic literature search was independently performed by 2 authors. The keywords used in our search strategy included: (NAC OR neoadjuvant) AND (bladder OR urothelial) AND (cancer OR tumor OR malignancy OR carcinoma) AND (biomarker). The primary outcome of interest was oncological outcomes in patients treated with NAC for UCB.

After removing duplicates, 2 independent reviewers screened the titles and abstracts. Any citation which either reviewer thought should be included or unclear for inclusion was identified for full text screening. Subsequently, reviewers reviewed full texts of eligible articles for final inclusion and data extraction. In cases of disagreement, the authors consulted with the co-authors, and final decisions were reached by consensus.

2.2. Inclusion and exclusion criteria

We included all non-randomized observational studies that reported on the prognostic value of blood-based biomarkers in UCB.

The PICO in this study was the following: patients treated for UCB with pretreatment laboratory blood-based abnormalities. The intervention included NAC for UCB. The control group included those patients without pretreatment laboratory blood-based abnormalities. The outcome included any measure of association between oncological outcomes and the candidate biomarker, the diagnostic performance of the biomarker.

We excluded reviews, letters, editorials, animal studies, study protocols, case reports, meeting abstracts, replies from authors, and articles not published in English. Furthermore, we excluded the studies that did not provide data regarding the oncological outcomes. References of all papers included were scanned for additional studies of interest.

2.3. Data extraction

Data extracted from each study were independently extracted by 2 independent reviewers. Extracted data included the following: first author's name, publication year, study design, demographics characteristics including age range, sample size, pathological T stage, follow-up duration, NAC regime, type of biomarkers, and conclusion. Subsequently, the hazard ratios (HR) and 95% confidence intervals (CI) of blood-based biomarkers associated with each outcome were retrieved.

2.4. Risk of bias assessment

The risk of bias was evaluated according to The Risk of bias in non-randomized studies of interventions tool. This tool is based on 7 domains that included bias due to confounding, participant selection, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result (Supplementary Table 1).

3. Results

The literature search identified 611 unique references. Among them, 233 records were removed due to duplication, and 261 articles were excluded due to unrelated outcomes during the screening process (Fig. 1). Of the 117 full-text articles assessed for eligibility, 107 were excluded based on the selection criteria.

Ten studies, including 966 patients who underwent NAC, were finally included in the present systematic review [22–31]. Characteristics of the studies are shown in Table 1. Three of the included studies had a prospective study design

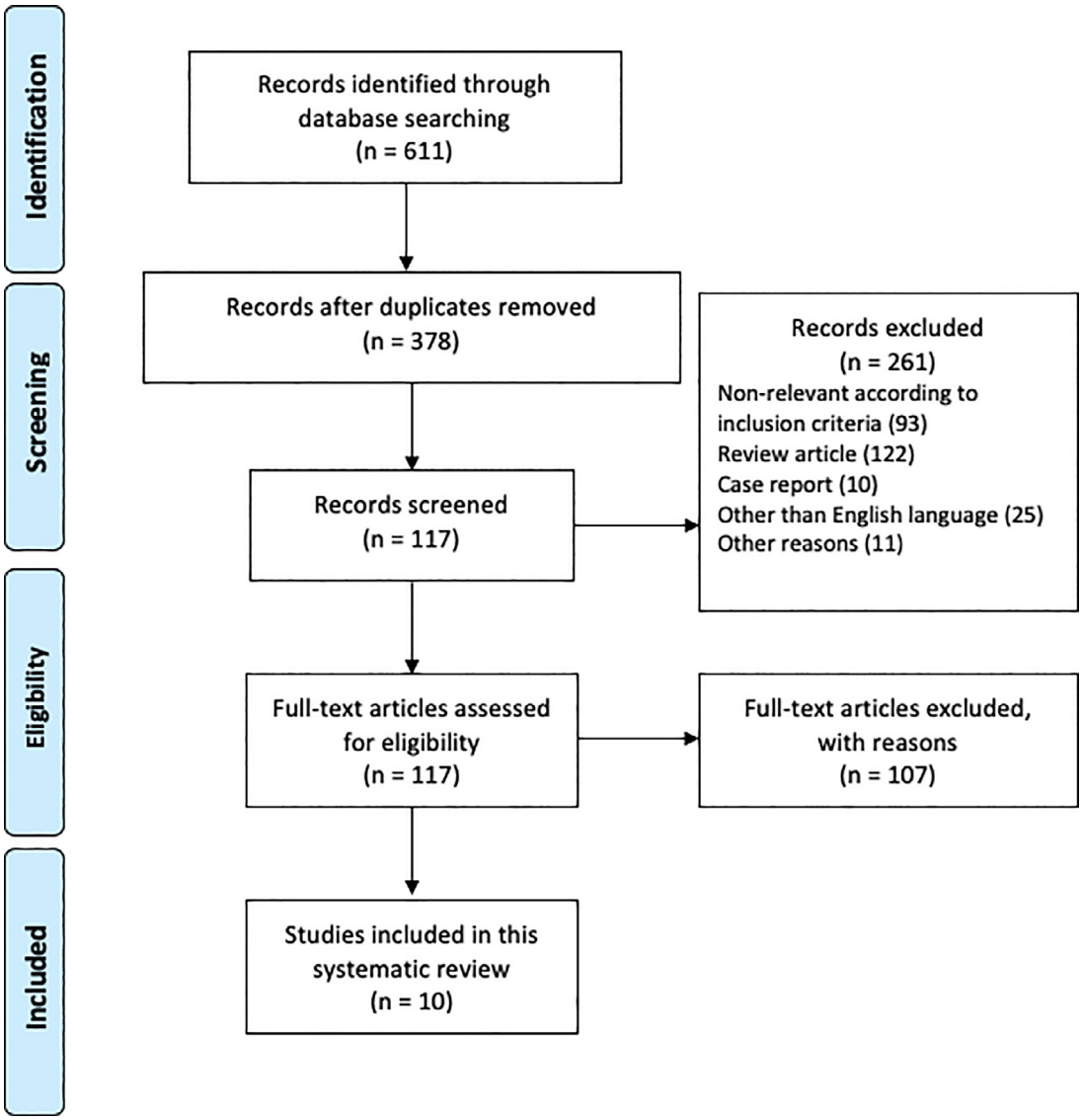

Fig. 1. Flow diagram of the study selection procedure for the systematic review

Table 1
Characteristics of included studies reporting oncologic outcomes in patients with bladder cancer who underwent neoadjuvant chemotherapy

Author, publication year	Study design	Number of NAC patients	Age, years (median, range)	pT Stage	Follow-up (median)	NAC	Type of markers evaluated (cut off values)	Significant outcomes
Soygur, 1999 [31]	R	30	49.2 (38–72)	T2-T4, N0/N+, M0	NR	M-VEC	CD22+, CD3+, CD4+, CD8+, CD57+, CD4/CD8 ratio	Pretreatment CD3+, CD4+, CD57+ cells ($P < 0.001$), and CD4+/CD8+ ratio ($P < 0.01$) - higher in patients who had remission than in those who had progression
Douglas, 2014 [22]	R	92	69 (48–84)	T0–4, N0, M0	NR	GC or GCb	hCG (2 IUl^{-1})	Low pretreatment hCG associated with improved OS (HR 3.41, 95% CI: 1.49–7.83, $P = 0.004$). Low pretreatment hCG was not associated with RFS ($P = 0.07$).
Seah, 2015 [23]	R	26	68 (49–85)	T0-T4, N0/N+, M0	11.8 months (4.8–30.9)	GC	NLR	Pretreatment NLR was not associated with pCR (HR 0.69, 95% CI: 0.36–1.32, $P = 0.26$)
Buisan, 2016 [24]	R	75	NR	T0-T4, N0/N+, M0	31 months	GC or GCb	NLR (2.5)	Pretreatment NLR associated with PR (OR 0.08, 95% CI: 0.64–0.99, $P = 0.04$), PFS (HR 1.25, 95% CI: 1.1–1.42, $P < 0.001$), CSS (HR 1.27, 95% CI: 1.11–1.44, $P < 0.001$), OS (HR 1.12, 95% CI: 1.01–1.23, $P < 0.021$)
Leibowitz-Amit, 2016 [25]	R	81	67.6 (41–87)	NR	32.3 months (4.8–111.4)	GC, GCb, MVAC, or others	Lymphocyte count, PLR, NLR, albumin, hemoglobin, neutrophil count, platelet count, WBC	Lymphocyte count associated with pCR: OR 3.63, 95% CI: 1.12–12.24, $P = 0.04$; PLR - OR 0.98, 95% CI: 0.97–0.99, $P = 0.04$; NLR - OR 0.48, 95% CI: 0.23–0.98, $P = 0.05$.
Ojerholm, 2016 [30]	R	113	NR	T2-T4aN0	18.6 years	MVAC	NLR	NLR did not predict for the response to NAC (HR, 1.01; 95% CI, 0.90–1.14; $P = 0.86$)
Kuwada, 2017 [26]	P	37	70 (44–80)	T0-T4, N0/N+, M0	28 months (6–61)	GC	PLR, NLR	PLR was associated with PR on multivariable analysis (HR 1.01, 95% CI: 1.00–1.03, $P = 0.048$). NLR was not associated with PR on univariable analysis (HR 1.23, 95% CI: 0.94–1.71, $P = 0.23$).
Bazargani, 2018 [27]	P	125	71 (34–93)	T0-T4, N0/N+, M0-1	631 days (IQR 162–1156)	GC, dose-dense MVAC, or others	CA-125 (35 U/ml), CA 19-9 (37 U/ml), CEA (3.8 ng/ml)	High pretreatment CA-125 associated with worse RFS ($P = 0.04$) and OS ($P = 0.05$); CA 19-9 - RFS ($P = 0.02$) and OS ($P = 0.03$). High CEA was not associated with worse RFS ($P = 0.27$) or OS ($P = 0.14$)

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Table 1 (*Continued*)

Author, publication year	Study design	Number of NAC patients	Age, years (median, range)	pT Stage	Follow-up (median)	NAC	Type of markers evaluated (cut off values)	Significant outcomes
Kaiser, 2018 [28]	R	351	NR	T2-4a, N0, M0	22.0 months (95% CI 14.9–30.0)	GC or GCb	NLR (3)	High NLR associated with DFS (HR 0.61, 95% CI: 0.44–0.84, $P < 0.001$), OS (HR 0.54, 95% CI: 0.38–0.77, $P < 0.001$)
Ornstein, 2018 [29]	P	36	68 (44–87)	T0-T4, N0/N+, M0	NR	GC, GCb, MVAC, or others	MDSC	PBMC %T-MDSC ($P = 0.006$) and PBMC %PMN-MDSC ($P = 0.01$) were negatively associated with pCR

DFS = disease-free survival; CEA = Carcinoembryonic Antigen; GC = gemcitabine/cisplatin; GCb = gemcitabine/carboplatin; hCG = human chorionic gonadotrophin subunit; MDSC = myeloid-derived suppressors cells; MVAC = methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin; M-VEC = methotrexate, vinblastine, epirubicin and cisplatin; NAC = neoadjuvant chemotherapy; NK = natural killer; NLR = neutrophil-lymphocyte ratio; NR = not reported; P = prospective; PBMC = peripheral blood mononuclear cells; pCR = pathologic complete response; PMN-MDSC = polymorphonuclear MDSC; PLR = platelet-lymphocyte ratio; PR = pathologic response; R = retrospective; RFS = relapse free survival; T-MDSC = total MDSCs; WBC = white blood cell count.

[26,27,29] and 7 were retrospective [22–25,28,30,31]. NAC regimens used in these studies were the following: gemcitabine/cisplatin (GC) [22–29]; gemcitabine/carboplatin (GCb) [22,24,25,28]; methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin (MVAC) [25,27,30]; methotrexate, vinblastine, epirubicin and cisplatin (M-VEC) [31].

1. *NLR*

Six studies provided data on the association between pretreatment NLR and oncological outcomes after NAC [23–26,28,30]. NLR predicted overall pathological response (PR) in 1 of the 2 studies [24,26]. Similarly, heterogeneous results were found regarding complete pathological response (pCR) (ypT0pN0), with only one study reporting a significant association between NLR and pCR [25], whereas 1 study did not [23].

In a prospective study of 37 patients treated with GC, Kuwada et al. found that NLR was not associated with PR on univariable analysis (HR 1.23, 95% CI: 0.94–1.71, $P = 0.23$) [26]. Similarly, Seah et al. reported that pretreatment NLR was not associated with pCR (HR 0.69, 95% CI: 0.36–1.32, $P = 0.26$) in 26 patients treated with GC for UCB [23]. However, their data suggested that a sustained decrease in inflammatory burden during NAC is associated with better outcomes. Contradictory results were found by Leibowitz-Amit et al. in a retrospective study of 81 patients treated with platinum-based NAC regimens (GC, GCb, MVAC, or others), where a lower pretreatment NLR was associated with a higher likelihood of achieving pCR (OR 0.48, 95% CI: 0.23–0.98, $P = 0.05$) [25]. Interestingly, they also showed a statistical difference between responders who had continuous lower NLR (pre-NAC, pre-surgery, post-surgery) compared to non-responders ($P < 0.01$).

The associations between NLR and overall survival (OS) were reported in 3 studies [24,28,30]. One study found associations between pretreatment NLR and progression-free survival (PFS) as well as cancer-specific survival (CSS) [24], while another study reported an association with disease-free survival (DFS) [28].

In a multivariable analysis of 75 patients receiving NAC (GC or GCb), Buisan et al. reported that NLR was a predictive of PR (OR 0.08, 95% CI: 0.64–0.99, $P = 0.04$), PFS (HR 1.25, 95% CI: 1.1–1.42, $P < 0.001$), CSS (HR 1.27, 95% CI: 1.11–1.44, $P < 0.001$), and OS (HR 1.12, 95% CI: 1.01–1.23, $P < 0.021$) [24]. Kaiser et al. reported that high NLR are associated with worse DFS (HR 0.61, 95% CI: 0.44–0.84, $P < 0.001$) as well as OS (HR 0.54, 95% CI: 0.38–0.77, $P < 0.001$) [28]. Controversial results were obtained during the secondary analysis of patients enrolled in SWOG 8710 [32]; Ojerholm et al. demonstrated that NLR is neither a prognostic nor predictive biomarker for treatment response in 113 patients receiving NAC for UCB [30].

In summary, for now, the utility of pretreatment NLR in patients treated with NAC is still controversial. According

to the currently available literature, pretreatment NLR in the NAC setting does not seem to clearly improve our prediction of pathological response, but it has a tendency to being useful prognosticating survival outcomes.

2. *PLR*

Two studies provided data on the association between pretreatment PLR and pathological outcomes after NAC [25,26]. While 1 study reported a significant association of PLR with PR [26], another 1 reported 1 with pCR [25].

Kuwada et al. found, in a logistic regression model, that high pretreatment PLR was associated with a poor PR in patients who received GC as NAC regimen for UCB (HR 1.01, 95% CI: 1.00−1.03, $P = 0.048$) [26]. Leibowitz-Amit et al. reported a significant association between pretreatment PLR and pCR (OR 0.98, 95% CI: 0.97−0.99, $P = 0.04$) [25]. Moreover, pretreatment PLR was different between responders and non-responders ($P < 0.01$), with ratios being lower in responders compared to non-responders at all 3-time points (pre-NAC, pre-surgery, post-surgery) and increasing with time in non-responders. Thereby, a higher pretreatment PLR level seems to be associated with a lower likelihood of achieving a pathological response after NAC. These data used to be confined in large prospective studies including data on the association between PLR and survival outcomes.

3. *Lymphocyte count*

Only one study provided data on the association between pretreatment lymphocyte count and outcomes after NAC [25].

They found that a higher pretreatment lymphocyte count was associated with a higher likelihood of achieving pCR (OR 3.63, 95% CI: 1.12−12.24, $P = 0.04$) [25]. There were no responders among the 9 patients with a baseline lymphocyte count of less than 1.3×10^9/l versus 14 responders among the 33 patients with a higher baseline lymphocyte count ($P = 0.016$). There was also a statistically significant difference in the lymphocyte count between responders and non-responders throughout time ($P = 0.003$); the responders exhibited a higher and constant mean lymphocyte count at all 3-time points (pre-NAC, pre-surgery, post-surgery), whereas the non-responders exhibited a trend to a decrease in total lymphocyte count across time.

4. *Lymphocyte subsets*

One study provided data on the association between B lymphocytes (CD22+), T lymphocytes (CD3+), T helper lymphocytes (CD4+), T suppressor lymphocytes (CD8+), natural killer (NK, CD57+), CD4/CD8 ratio and progression after NAC [31]. Another study assessed the association between myeloid-derived suppressors cells (MDSC) and pCR after NAC [29].

In a study by Soygur et al., in patients who experienced a remission, the pretreatment values of CD3+, CD4+, CD57+ cells, and the ratio of CD4+/CD8+ cells were significantly higher than those in patients who experienced progression (all $P < 0.01$) [31]. The percentage of pretreatment peripheral blood NK cells (CD57+) seemed to be the most sensitive and specific variable for predicting clinical progression after NAC ($P < 0.001$).

MDSCs are a phenotypically different population of bone marrow-derived cells that play an important role in tumor progression based on their immunosuppressive and proangiogenic properties [33]. Ornstein et al. reported that both peripheral blood mononuclear cells (PBMC) total MDSC ($P = 0.006$) and PBMC polymorphonuclear MDSC ($P = 0.01$) were negatively associated with pCR in 36 patients who underwent NAC with GC [29].

5. *Human chorionic gonadotrophin b subunit (hCG)*

One study provided data on the association between hCG and OS as well as relapse free survival after NAC [22]. In a study of 92 patients treated with preoperative GC or GCb for UCB, low pretreatment hCG was associated with improved OS (HR 3.41, 95% CI: 1.49−7.83, $P = 0.004$) [22]. In contrast, low pretreatment hCG (<2 IUl-1) was not associated with higher relapse free survival ($P = 0.07$).

6. *Epithelial tumor markers*

One study provided data on the association between serum levels of epithelial tumor markers such as carbohydrate antigen 125 (CA-125), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA) and OS as well as recurrence-free survival (RFS) after NAC [27].

Bazargani et al. reported that high pretreatment CA-125 (with a cut-off of 35 U/ml) was associated with worse RFS ($P = 0.04$) and OS ($P = 0.05$) [27]. Similarly, CA 19-9 > 37 U/ml was also associated with both worse RFS ($P = 0.02$) and OS ($P = 0.03$). However, high CEA was neither associated with RFS ($P = 0.27$) nor OS ($P = 0.14$).

7. *Other blood-based biomarkers*

One study provided data on the association between hemoglobin, albumin, white blood cells (WBC), neutrophil count, and platelet count with oncologic outcomes after NAC [25].

Leibowitz-Amit et al. found that the pretreatment levels of neither hemoglobin, albumin, WBC, neutrophil count, nor platelet count were significantly associated with pCR after platinum-based NAC (all > 0.05) [25].

4. Discussion

The present systematic review of the available pretreatment blood-based biomarkers that may help select patients

who are most likely to benefit from NAC generated several important findings.

First of all, there is no clear benefit of using NLR as a predictive biomarker for PR and pCR after NAC. Despite finding a statistically significant correlation between higher pretreatment NLR and worse PFS, CSS, OS, and DFS, its significance/ value remains to be established. It should be noticed that there is no clearly established and accepted cut-off value for NLR, resulting in heterogeneity in studies; some of the studies even investigated NLR as a continuous variable. Taken together, the heterogeneity of the studies and the contradictory results put the value of NLR into question. Moreover, the question if thepCRis an appropriate endpoint to predict NAC response is quite debatable. It has come under recent scrutiny as a surrogate endpoint in patients with UCB, given thatpCRmay reflect the biology of disease and quality of TURBT in addition to NAC response. However, a recent meta-analysis suggested thatpCRmight be a surrogate of better survival outcomes such as OS or RFS in patients treated with NAC for UCB [34].

According to the currently available literature, a higher pretreatment PLR seems to be associated with a lower likelihood of achieving PR or pCR. Lymphopenia may also impede NAC response, while there is no clear predictive benefit to hemoglobin, albumin, WBC, neutrophil count or platelet count. The main limitations of these studies were their short follow up period, their retrospective nature, and their small sample size that limit conclusive probing of clinically significant associations.

The quality and quantity of the data on the ability of lymphocyte subsets (CD3+, CD4+, CD57+ cells, the ratio of CD4+/CD8+), MDSC, hCG, and epithelial tumor markers (CA-125, CA 19-9, CEA) to predict oncological outcomes in patients treated with NAC for UCB are limited. There was only 1 study on each of these biomarkers. Moreover, conventional multivariable analyses are not sufficient to demonstrate improved prediction of outcomes [20]. Predictive models, including new biomarkers, need to show clinically significant performance improvement to claim any real benefit. It can be supported by using such statistical methods as Harrell's concordance index and decision curve analysis [19,20].

Only 1 study included in our systematic review assessed biomarkers' levels at 3-time points such as pre-NAC, pre-surgery, and post-surgery [25]. All the others did not collect longitudinal values during the treatment and follow-up. However, it was shown that several preoperative serum biomarkers were strongly associated with an increased risk of cancer-specific mortality in patients with UCB [35]. Chemotherapy and surgery both impact inflammation and immunologic status; their combination might also modify the serum biomarkers largely, leading to these controversial results. That is why we believe that a direction for further research should be to assess the modifications of the biomarkers at certain time points. That may help our understanding and result in an enhanced predictive value.

The main strength of the present systematic review is that it is the first study summarizing the available serum biomarkers assessed in the NAC setting for UCB. Nevertheless, there are several potential limitations. First, the inconsistencies in evaluation of the serum biomarkers among the enrolled trials could lead to some potential confounding and bias. Second, we did not review the letters, editorials, animal studies, study protocols, case reports, reviews, replies from authors. We also excluded data from meeting abstracts as well as articles not published in English. The third limitation is that this review highlights the retrospective and heterogeneous nature of most of these studies based on a single-center cohort. Fourth, the small cohort size of most of the included studies may have limited their power to find a statistically and/or clinically significant associations. Therefore, well-designed comparative trials with larger cohorts are required to validate the most promising findings of the present systematic review.

5. Conclusion

Current literature suggests that several pretreatment blood-based biomarkers could be used to assess response to NAC in UCB. The easy access and low cost of these biomarkers would help to implement them in daily practice after being tested in a phased validation strategy. However, their role as an adjunct to established prognostic markers for clinical decision-making requires further external validation and clinical utility assessment.

Ethical standards

Not applicable.

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Supplementary materials

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