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The red cell distribution width as a prognostic indicator in upper aerodigestive tract (UADT) cancer: A systematic review and meta-analysis

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ABSTRACT

Purpose: The aim of this systematic review and meta-analysis was to investigate the relationship between the Red Cell Distribution Width (RDW) and prognosis in upper aerodigestive tract (UADT) cancer.
Methods: PubMed (via the web), Embase, Scopus, and the Cochrane Library were searched. A systematic review and meta-analysis was done to generate the pooled hazard ratios (HR) for overall survival (OS), disease specific survival (DSS), and recurrence free survival (RFS).
Results: Our analysis included the results of 4200 patients in 8 cohorts. The pooled data demonstrated that an elevated RDW was associated with significantly poorer OS (HR: 1.44, 95% CI: 1.13–1.83), RFS (HR: 1.43, 95%CI: 1.13–1.82). The DSS result had high heterogeneity and 95% CI was not pooled.
Conclusions: An elevated RDW may be an indicator of poor prognosis in UADT cancers in certain populations. Further research is needed to confirm this effect.

1. Introduction

Cancers of the upper aerodigestive tract (UADT) consist of tumors in the head and neck and its associated subsites, which include the oral cavity, nasal cavity, paranasal sinuses, oropharynx, nasopharynx, larynx, and the esophagus. According to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute UADT cancers constitute approximately 4% of all malignancies [1]. The vast majority of cancers at these sites are squamous cell carcinomas; while the exact cause is unknown, risk factors include, alcohol, tobacco use, HPV, and possible poor hygiene [1]. Upon diagnosis, local treatment with surgery and/or radiation therapy is often the first line of treatment [2].

Traditionally, prognostication of these UADT cancers is primarily based on the TNM staging of the tumor. Arguably, the main downside of the TNM staging system is that is takes into account superficial tumor characteristics, but omits patient specific factors that could have a bearing on prognosis as well. For example, the latest AJCC staging system for head and neck cancer (HNC) has been updated to include HPV status in oropharyngeal tumors. In addition to HPV, there has been increasing interest in easily obtained routine blood markers that have shown evidence in cancer prognostication. These markers are hypothesized as crude features of the underlying interaction between the tumor microenvironment and the host immune system [3–5]. Such biomarkers, if fully validated, might have utility in stratifying patients in rationalized patient-centric treatment regimens.

One biomarker recently reported as having prognostic utility is the red cell distribution width (RDW). The RDW has been shown in a prior meta-analysis to be a useful prognostic indicator of survival in other cancers [6]. To the best of our knowledge, this is the first meta-analysis specifically reporting the potential utility of the RDW as a prognostic indicator in UADT cancers. Thus, the aim of our study was to investigate if the RDW is a prognostic indicator in UADT cancers.

2. Materials and methods

2.1. Design

Our search was performed in accordance with the Cochrane Handbook for DTA Reviews chapter on searching [7]. Additionally, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines to identify, screen, and describe the protocols used in this systematic review [8]. We also followed the Meta-analysis Of Observational Studies in Epidemiology

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(MOOSE) Checklist [9].

We designed the search strategy in collaboration with a librarian at the Zucker School of Medicine (WH). Our protocol was designed a priori and prospectively registered in an online systematic review database (PROSPERO 2018 CRD42018087533) [10]. Since this study was a systematic review and meta-analysis, registration with our Institutional Review Board (IRB) was not required.

2.2. Search strategy

PubMed (via the web), Scopus, Embase, and the Cochrane Library were searched on 2/6/18. We searched all databases from their inception to the present, limited to articles written in English, and excluded grey literature. Variations of the following concepts were used: red cell distribution width, cancer, and regions of the head and neck or esophagus. The full search strategy may be found in the supplementary materials.

2.3. Article selection

Articles were selected independently by two of the authors (TT, YB) in two phases. In the first phase we screened a list of titles and abstracts for full-text retrieval. During the first phase (title and abstract screening), our inclusion criteria included any study that reported a description of RDW in UADT cancers, either in the title or abstract. If the content of the abstract was not clear, we selected the study for full-text review. Articles that passed the first phase of screening were selected for full-text retrieval, and were assessed in a second phase of screening.

In the second phase, we screened full text articles using pre-determined inclusion and exclusion criteria [10]. Inclusion criteria: (1) Article reports on prognostic impact of peripheral RDW in UADT cancers; (2) RDW treated as categorical variable; (3) RDW collected prior to treatment; (4) available RDW Hazard Ratio (HR)/Risk Ratio (RR) for Overall Survival (OS), Disease specific survival (DSS), with or without Disease Free Survival (DFS), with or without Progression free survival (PFS); (5) 95% confidence interval (CI) for survival statistic, with or without the *p*-value; (6) available as full text publication; (7) English Language; (8) Clinical trial, cohort, case control. Exclusion criteria: (1) Case report, conference proceeding, letters, reviews/meta analyses; (2) thyroid, endocrine and nasopharyngeal tumors; (3) animal studies; (4) laboratory studies; (5) duplicate literature and duplicate data; when multiple reports describing the same population were published, only the most recent or complete report was included; (6) incomplete data (No RDW HR for OS/DSS). Disagreements were resolved via consensus.

The PRISMA flow chart for this systematic review can be found in Fig. 1. The initial search performed using our search strategy (Supplementary materials) yielded a total of 440 results. After removing duplicates, 420 results remained. The first phase of screening was performed one the titles/abstracts, which reduced the number of articles to 15. The level of agreement was good with a Kappa statistic of 0.74. The second phase of screening resulted in 7 papers for the meta-analysis. The agreement was good with a Kappa of 0.70. The list of excluded papers with the reasons for exclusion can be found in the Supplementary Materials.

2.4. Quality assessment

Two authors (YB, ST) jointly assessed the risk of bias in the included papers. The assessment was made using the Quality In Prognosis Studies Tool (QUIPS) [11]. QUIPS is based on six domains: study participation, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain contained a checklist of three to nine subdomains, which were used to render a score of low, moderate, or high risk of bias for the entire main domain. A detailed breakdown of the scoring criteria and subdomains is included with the Supplementary materials. Disagreements in scoring of the domains were reconciled with a third author (TT).

2.5. Data extraction

Data forms were developed a priori as recorded in the PROSPERO registry [10]. Two authors (TT, YB) jointly reviewed all of the full text articles together for the data extraction process. If there were disagreements about data points, a third author (ST) was consulted to adjudicate and resolve the disagreement. The following data points were collected: First author's name; Year of publication; Country (region) of the population studied; Sample size; Age; Follow-up period; Tumor stage; Survival data HR/RR OS, DSS, RFS, DFS, PFS, with the associated 95% CI, p-value; Survival data reported with univariate or multivariate analysis; Cut-off value used to define “elevated RDW”; Method of obtaining the cut-off value. For the analysis of the relationship between RDW and clinicopathological parameters, HR/RR and 95% CI were combined as the effective value. If several estimates of RDW HR were reported in the same article, we chose the most powerful one (multivariate analysis was superior to univariate analysis, and the latter one weighted over unadjusted Kaplan–Meier analysis).

2.6. Statistical analysis

The logarithm of the HR with Standard Error (SE) was used as the primary summary statistic. To obtain the log[HR] and SE, the HR with 95% CI was extracted directly from the studies. Additional calculation to obtain the HR was required if the study reported the reciprocal of the HR. Estimates of log[HR] were weighted and pooled using the generic inverse-variance [7]. Because of anticipated heterogeneity, a more conservative approach applying the random effects model (DerSimonian and Laird method) was chosen for all analyses. Forest plots were constructed for all outcomes displaying the random-effects model of the summary effect measure and 95% CI. Heterogeneity was assessed using Cochran's Q and Higgins' I^2. A Cochrane's Q p-value of < 0.1 and an $I^2 > 50\%$ were considered as markers of significant heterogeneity. Sensitivity analysis was also performed for all outcome measures. For survival statistics that showed heterogeneity, we did not report the confidence interval but instead report the *95% Prediction Interval* (*95% PI*). As opposed to the *95% CI*, the *95% PI* takes into account heterogeneity and is the statistic of choice when interpreting pooled results that show heterogeneity [12,13]. All analyses were done using the RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark) [14] and Meta Essentials (ERASMUS Research Institute, Rotterdam, Netherlands) [15]. All statistical tests were two-sided, and a p-value of < 0.05 was considered statistically significant. No correction was made for multiple testing. We intended to assess publication bias using funnel plot techniques and Egger's regression, as appropriate given the known limitations of these methods.

3. Results

3.1. Study characteristics

A total of 7 studies (8 cohorts) published between 2015 and 2017 were included in our meta-analysis, with sample sizes ranging from 144 to 1822 (Fig. 1) [16–22]. Characteristics of the included studies featuring tumor stage, site, and further details are in Table 1. Six of the studies were from China, and one from Japan and Thailand. One of the studies analyzed men and women separately, and is thus denoted as Hu1 and Hu2 [18]. Of all the studies, one of them was based on prospectively collected data [18]. With regards to the reported survival outcomes, 5 reported DSS, 3 reported OS, and 3 reported RFS. RDW cutoff ranged from 12.2% to 15% (Median 13.6%). HR was reported through multivariate analysis in all except one study [19]. Publication