

**PREDICTIVE VALUE AND CLINICOPATHOLOGICAL FEATURES OF TUMOR
INFILTRATING LYMPHOCYTES IN NASOPHARYNGEAL CARCINOMA: META-
ANALYSIS.*****Birhanu Aberha Berele, MMed¹, Yang Guifang (MD)² and Malyn M. L. K. Antoine, MD³**¹Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, China.²Department of Pathology, Zhongnan Hospital of Wuhan University.³Department of Endocrinology, Zhongnan Hospital of Wuhan University, Wuhan, China.***Corresponding Author: Birhanu Aberha Berele**

Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, China.

Article Received on 07/12/2020

Article Revised on 28/12/2020

Article Accepted on 17/01/2021

ABSTRACT

Objective: The aim of the study was to evaluate the predictive value and clinicopathological features of tumor infiltrating lymphocytes (TILs) in nasopharyngeal carcinoma (NPC) patients. **Method:** Meta-analysis was performed on eligible studies that was identified by systematic searching in PubMed, PMC and web of Science databases. Studies that reported survival data were included and extracted. All statistical analysis was conducted by STATA 16.0 software. **Result:** In late stage patients, higher number of TILs was associated with worse disease free survival (DFS) (HR=2.62; CI=1.80-3.80; P=0.003) and overall survival (OS) (HR=2.49; CI=1.73-3.60; P=0.002). For >45 years old patients, while TILs also predicted statistical significant poor prognosis for OS (HR=1.29; CI=0.99-1.68; P=0.05); however, the result didn't show statistical significant relationship for DFS (HR=1.15; CI=0.92-1.45; P=0.09). Moreover, although higher TILs expression had better prognosis for females than males, but the association wasn't statistical significant (p=0.07). **Conclusion:** In late stage patients, high TILs expression was correlated with poor prognosis. This suggest that advanced stage NPC patients might be benefited from immunotherapy than early stage patients.

KEYWORDS: TILs, clinicopathological features, nasopharyngeal carcinoma.**INTRODUCTION**

Nasopharyngeal carcinoma (NPC) is a common malignancy in southern China and East Asia.^[1,2] The distinct geographical distribution of the disease suggests the combination of Epstein Barr virus (EBV) infection, genetic and environmental factors might contribute for nasopharyngeal carcinoma pathogenesis.^[2] Due to highly invasive and metastatic potential of the disease the, NPC has unfavorable prognosis.^[3-5] Although a great improvement has been seen regarding chemoradiotherapy, however about 20-30 % of patients still would recur.^[6] Tumor infiltrating lymphocytes (TILs) are becoming a powerful prognostic tool to guide treatment.^[7-9] Thus, having detail knowledge of the association between TIL and different clinicopathological characteristics of NPC patients such as age, sex and stage are important for appropriate treatment strategies and reduce drug toxicity related quality of in NPC patients. Although many studies evaluated clinicopathological features of TILs in NPC patients, however they are controversial. Therefore, we performed meta-analysis study to settle this argument.

MATERIALS AND METHODS

The search strategy was by systematically searching in PubMed, PMC and Web of Science databases to identify and include articles based on the eligibility criteria we set.

The inclusion criteria to include in our meta-analysis was: (a) original articles; (b) that reported the prognostic association of TILs with clinicopathological parameters in NPC patients in the form of hazard ratio (HR), or that reported in the form of Kaplan Meier (KM) curve. We exclude studies that didn't provide enough data to analysis such as case reports and non-English publications.

The retrieved articles were sorted by EndNote version 7.0 software, and the data extraction was conducted by two pathologist.

The following data were extracted: name of first author, publication year, sample size, age, sex, stage and subtype of NPC.

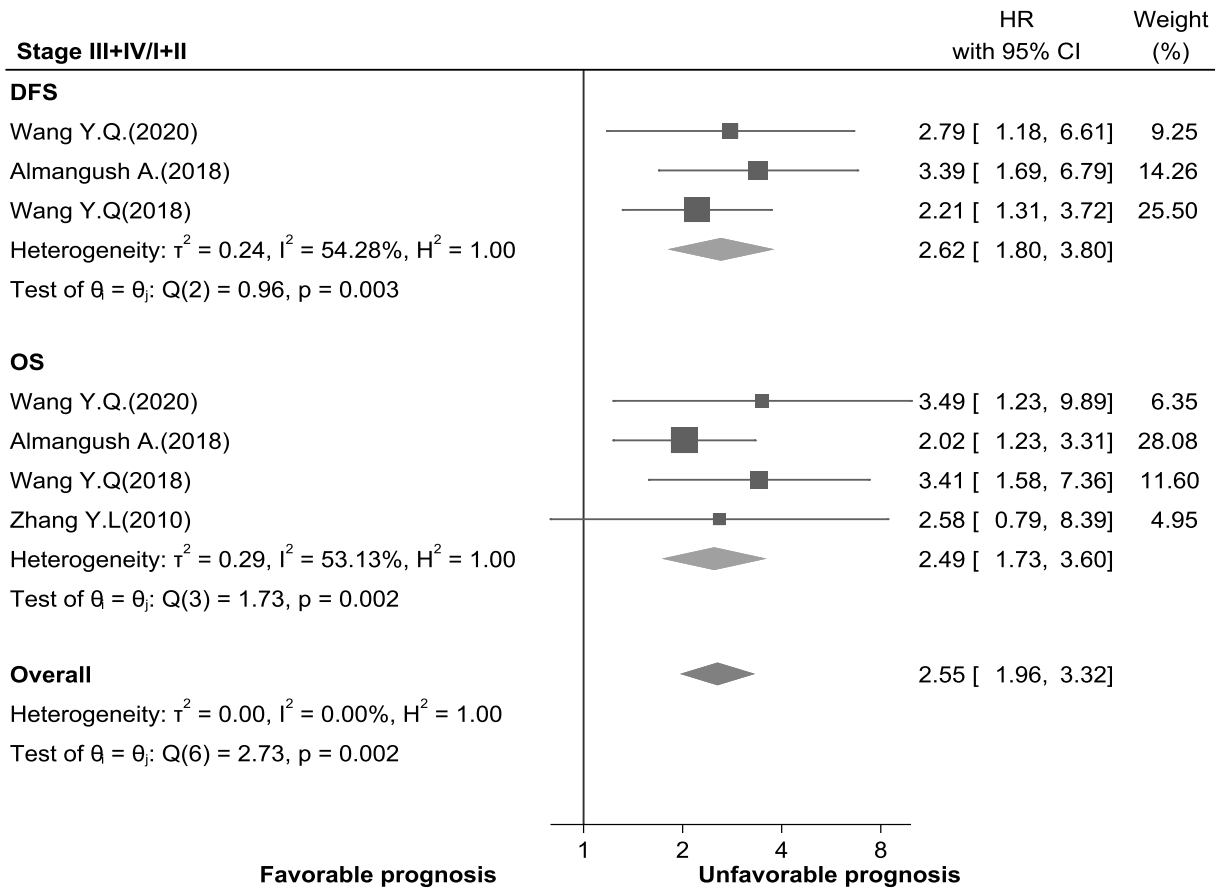
All statistical analysis was performed by STATA version 16.0 software. Heterogeneity among studies was measured by Chi-square (I^2), where <50% were

considered less heterogeneous. Fixed effect model was used for homogenous, otherwise random effect model. P-value <0.05 was considered as statistical significant.

RESULTS

The relationship between TILs and clinopathological features was analyzed from eight included studies.^[10-17] Here, we assessed the correlation between TILs density and patient outcomes in different disease stages. In late stage patients, higher number of TILs was associated with worse disease free survival (DFS) (HR=2.62; CI=1.80-3.80; P=0.003) and overall survival (OS)

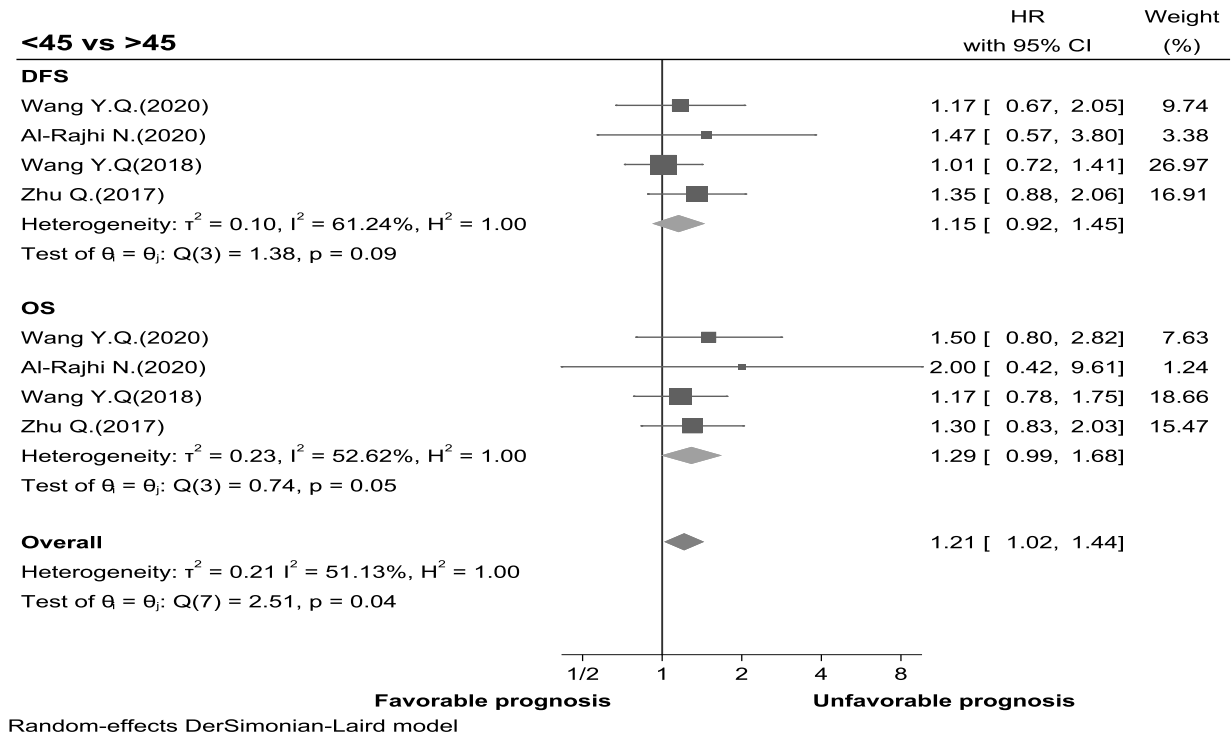
(HR=2.49; CI=1.73-3.60; P=0.002) (**Fig. 1**). In contrast, the pooled result didn't show statistical significant higher risk relationship of TILs with >45 years old patients for DFS (HR=1.15; CI=0.92-1.45; P=0.09) (**Fig. 2A**). However, TILs predicted statistical significant poor prognosis for OS (HR=1.29; CI=0.99-1.68; P=0.05) for >45 years old patients (**Fig.2A**). Although higher TILs expression had better prognosis for females than males, but it didn't reach statistical significant correlation (p=0.07) (**Fig.2B**).



Random-effects DerSimonian-Laird model

Figure 1. Forest plot the relationship between tumor infiltrating lymphocytes and stag for disease free survival (DFS) and overall survival (OS).

A



B

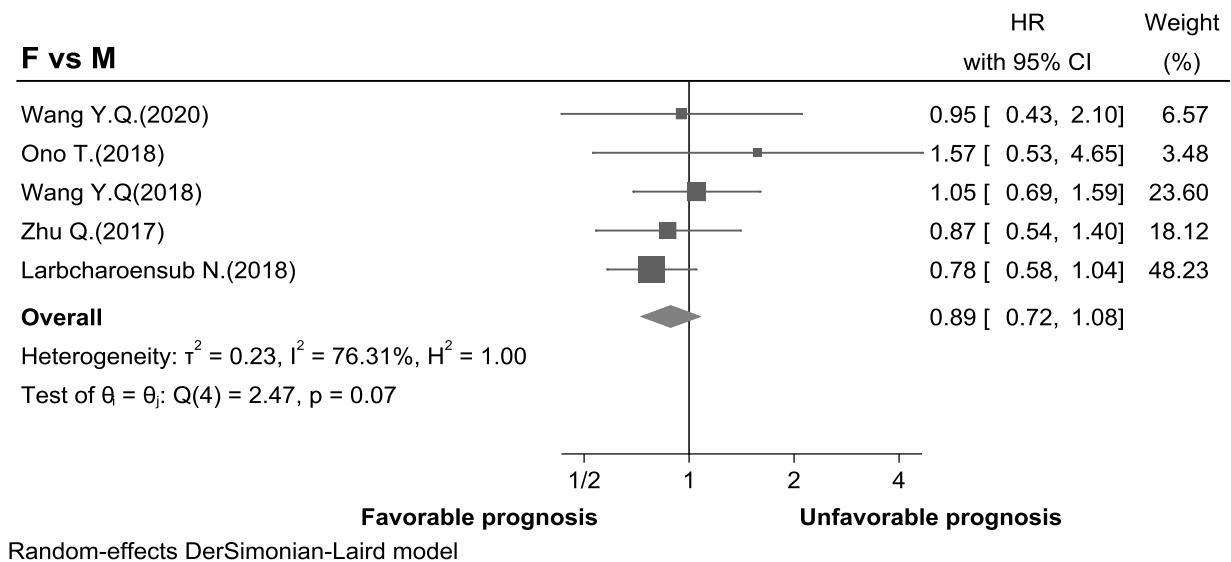


Figure 2. Forest plot the relationship between tumor infiltrating lymphocytes and (A) age; (B) sex.

DISCUSSION

To date, an increasing evidence reveals that a relationship exists between TILs and cancer patient’s outcome. Therefore, although a number of studies evaluated the correlation of TILs and NPC patients, however, remained controversial. Thus, we performed meta-analysis to settle the argument.

Our meta-analysis result indicated that in late stage patients, high TILs expression was correlated with poor prognosis. This suggest that advanced stage NPC patients might be benefited from immunotherapy than

early stage patients. Similarly, positive TILs expression in > 45 years old patients also could predicted relatively worse OS, but not DFS. This implies that immune cells could also be targeted in those category of patients to selectively apply immunotherapy to reduce drug toxicity related side effects. Our result is partially consistent with previous studies on different cancers.^[18-20]

There were some limitation of the present study. First, non-English articles weren’t included in our analysis. Second, due to insufficient data, we didn’t evaluate the subtype of NPC and subtype of TILs that could affect the

trend in prediction and prognosis of the disease. However, these clinicopathological feature findings we found are important for patient selection.

In conclusion, TILs were correlated with clinicopathological parameters and was potential prognostic predictors for NPC patients. Particularly, in late stage patients, high TILs expression was correlated with poor prognosis which suggests that this category of patients could be benefited from immunotherapy.

ACKNOWLEDGMENT

N/A

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