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Neutrophil/lymphocyte ratio as a prognostic factor in biliary tract cancer ☆

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Abstract ***Background:*** Biliary tract cancers (BTCs) include intrahepatic (IHC), hilar, distal bile duct (DBD) and gallbladder carcinoma (GBC). Neutrophil/lymphocyte ratio (NLR), a marker of host inflammation, is prognostic in several cancers but has not been reviewed in large BTC series, or advanced BTC (ABTC) at diagnosis.

Patients and methods: Baseline demographics and NLR at diagnosis were retrospectively evaluated in 864 consecutive patients with BTC treated from January 1987 to December 2012. The association between NLR and overall survival (OS) was determined using a multivariable Cox proportional hazards model.

Results: Eight hundred and sixty-four patients were included in the analysis, of which 62% had ABTC and 38% had surgery with curative intent. Median age was 65 years, 444 (51%) were male and 727 (84%) had performance status (PS) $\leqslant$2. A NLR $\geqslant$3.0, PS >2, IHC primary, stage, lack of surgery, haemoglobin <110 g/L and albumin <40 g/L were associated with significantly worse OS on multivariable analysis. A NLR $\geqslant$3.0 was an independent prognostic factor for OS for the entire cohort; median OS was 21.6 months versus 12.0 months for patients with NLR <3.0 versus NLR $\geqslant$3.0 respectively (adjusted hazard ratio (HR)-1.26, 95% confidence interval (CI); 1.06–1.50, $P = 0.01$). NLR was also prognostic in patients with ABTC (HR-1.26, 95% CI; 1.02–1.56, $P = 0.035$) and hilar cancer: overall group ($N = 149$)

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(HR-1.70, 95% CI; 1.10–2.50, $P = 0.01$) and advanced group ($N = 111$) (HR-1.57, 95% CI; 1.04–2.44, $P = 0.048$).

Conclusion: Baseline NLR is a readily available and inexpensive prognostic biomarker in patients with BTC and likely warrants validation in large prospective clinical trials.

1. Introduction

Biliary tract cancers (BTCs) encompass both gallbladder carcinoma (GBC) and cholangiocarcinoma, referring to cancers arising in the intrahepatic (IHC), hilar or distal bile duct (DBD). There are important differences in clinico-pathological characteristics and prognostic factors in this group of diseases despite sharing a similar anatomic origin in the biliary system [1,2].

Acute inflammation mediates host defence against infections but chronic inflammation that persists for prolonged periods may predispose to various chronic illnesses, including cancer [3]. A number of risk factors for BTC share a common theme of chronic tissue damage/inflammation such as gallstones, chronic hepatitis, primary sclerosing cholangitis and liver fluke infection [4,5].

The neutrophil/lymphocyte ratio (NLR), a marker of host inflammation, is prognostic in several cancers, its elevation being associated with worse overall survival (OS) [6–8]. In addition, elevated pre-treatment NLR has also been reported as a potential biomarker of worse response to first-line chemotherapy in advanced non-small cell lung cancer [9].

Eastern Cooperative Oncology Group Performance Status (ECOG PS), metastatic disease, neutrophilia, anaemia and thrombocytosis are reported predictors of survival in BTC with baseline liver function variables having no effect [10]. The NLR has been studied as a prognostic factor in patients with BTC having surgery for curative intent [11,12], but has not been reviewed as a prognostic factor in large studies of patients with advanced BTC (ABTC) at diagnosis.

The aim of this study was to investigate the prognostic role of NLR in patients with BTC and association of NLR with progression free survival (PFS) or likelihood of response to first-line chemotherapy in patients with ABTC. It was hypothesised that elevated baseline NLR is prognostic of worse OS, PFS and response to chemotherapy in ABTC.

2. Patients and methods

2.1. Study population and data collection

Electronic charts of consecutive patients with BTC treated at Princess Margaret Cancer Centre, Toronto (January 1987–December 2012) were reviewed. There were two groups of patients; those having surgery with curative intent and those referred to Medical Oncology with ABTC. Institutional review board approval was obtained for this study.

Baseline demographics; age, gender, ECOG PS, site of primary (GBC, DBD, hilar or IHC), stage, surgery with curative intent, receipt of chemotherapy (adjuvant or palliative), haemoglobin, platelets, albumin and peripheral blood NLR at diagnosis (prior to surgery for the surgical cohort, at diagnosis for the ABTC group) were evaluated. Stage classification was based on pathological findings and documented according to the 7th edition Tumour-Node-Metastasis, American Joint committee on Cancer staging system. Ampullary tumours were not included because of potential different biology [13]. Patients with symptoms of cholangitis were excluded. C-reactive protein/carbohydrate antigen (CA 19-9) were not measured routinely at diagnosis and not included in this retrospective analysis.

The NLR was defined as the absolute neutrophil count in peripheral blood divided by the absolute lymphocyte count.

2.2. Statistics

Data on categorical variables were reported as frequencies + percentages. Analyses were initially conducted for whole cohort of patients, then repeated in two independent cohorts of patients; those having surgery with curative intent and patients with ABTC. Patients presenting with ABTC who had been included in the surgical cohort within this study initially, were analysed as per their primary presentation. Univariable analysis on categorical variables was performed using Chi-square test. Continuous variables were described as median (interquartile (IQ) values or range). Comparisons between groups of interest were performed through *T*-test or analysis of variance. Long term follow-up data were analysed and reported as OS, defined as percentage of people in the cohort who are still alive from date of diagnosis with censoring at last date of contact for those alive at data cut-off (December 2012). The OS estimates were evaluated using the Kaplan–Meier method. The log-rank test was used to report significance between groups. In patients treated with first-line palliative chemotherapy in the ABTC group, PFS was calculated from the date of cycle 1, day 1, chemotherapy to the date of disease progression as reported on imaging or date of death from any cause, whichever occurred first. Best