CLINICOPATHOLOGICAL RISK FACTORS FOR BRAIN METASTASIS IN BREAST CANCER PATIENTS: A META-ANALYSIS

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BACKGROUND: Breast cancer brain metastasis (BCBM) has an incidence rate of 5.1% among Breast Cancer (BC) patients. In BCBM, cancerous cells come from a primary tumor that implant and grow in the brain leading to potentially lethal neurologic symptoms and signs. With more clinical options and therapeutic strategies becoming available, a multidisciplinary approach to treatment is needed in order to best meet BCBM patients' needs, however, systematic guidelines for the screening of high-risk asymptomatic patients are still lacking and the BCBM diagnoses are performed only after symptoms manifestation. Therefore, understanding the clinical and pathologic drivers of BCBM aids in improving medical interventions by guiding future research directions. This study aims to determine the clinicopathological risk factors of brain metastasis (BM) among BC patients.

METHODS: Retrospective cohort studies on the clinicopathological characteristics of BM versus non-BM (NBM) patients were retrieved through reputable search databases. Review Manager version 5.4.1 was used for statistical analyses. In the presence of heterogeneities, a pragmatic approach was undertaken to employ both random-effects (RE) and fixed-effect (FE) meta-analyses. Due to the presence of heterogeneities and funnel plot symmetry, random-effect models were chosen. The odds ratio (OR) was employed to compare the incidence of clinicopathological risk factors associated with BCBM patients versus NBM patients. The statistical significance of the pooled effect estimates was examined by the Z-test. Interstudy variations and heterogeneities were estimated using Cochran's Q-statistic with $P < 0.05$ indicating a statistically significant heterogeneity. Funnel plot asymmetry was estimated via visual inspection. The risk of bias and the quality of studies was assessed at a study level using the ROBINS-I tool.

RESULTS: A total of four (4) retrospective cohort studies were included in the analyses. Random-effects meta-analyses with $i^2 < 50\%$ ($P > 0.05$) had shown significant association ($P < 0.05$) on the increased incidences of BCBM development for HER2+ expression [OR: 2.43, 95% CI: 1.88 – 3.12, $P < 0.00001$] and for pre-menopausal status [OR: 1.77, 95% CI: 1.13 – 2.76, $P = 0.01$]. Fixed-effect meta-analyses had shown a significant association ($P < 0.05$) on the decreased incidence of BCBM development for TNBC disease [OR: 0.66; 95% CI: 0.47 – 0.92; $P = 0.02$]. The risk of bias was low to moderate in the majority of studies.

CONCLUSION: HER2 positivity and pre-menopausal status are risk factors for increased BCBM development while the absence of regional lymph node metastases and ILC findings are less likely to progress to BCBM. Higher T and N categories, higher histological grade, ER negativity, and PR negativity may be associated with higher risks of BCBM while lower T categories, HER2 negativity, and TNBC may likely be associated with less BCBM development. More powerful relevant and upcoming randomized clinical trials with larger sample sizes among BCBM patients versus non-BM patients must be made exploring certainty on the clinicopathological factors contributing to BM among BC patients.

Keyword/s: risk factors, breast cancer, brain metastasis