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Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as Prognostic Markers in HER2-Positive Early Stage Breast Cancer

D. Kelly, G. Gullo, R.A. Rahman, L. Prior, J. Walshe, J. Crown

St. Vincent's University Hospital, Dublin.

Abstract

Background

The objectives of our study were to evaluate the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in patients with locally advanced Her-2 breast cancer treated with neo-adjuvant chemotherapy and to correlate NLR and PLR with disease free survival (DFS) and overall survival (OS).

Methods

This was a retrospective, single centre study of locally advanced Her 2+ breast cancer who received neo-adjuvant chemotherapy. The survival benefit of NLR and PLR at baseline with respect to OS and PFS were examined with kaplen-meier curves with log-rank testing. The prognostic value of NLR and PLR were examined with univariate analyses using the cox proportional hazard regression model for hazard ratio (HR) with respect to OS and DFS.

Results

Among 156 women, patients with an NLR <2.5 at baseline had significantly improved DFS (p=0.02) and OS (p=0.04) compared to those who had a baseline NLR >2.5. Patients with a PLR <150 at baseline had significantly improved OS (p=0.04) compared to those who had a PLR>150 at baseline, however, there was no statistically significant improvement in DFS in the PLR >150 group.

Conclusion

Baseline NLR >2.5 and PLR >150 are adverse prognostic features in locally advanced Her-2 breast cancer patients receiving neoadjuvant chemotherapy.

Introduction

HER2 amplified breast cancers have traditionally exhibited aggressive biological behaviour. However, the advent of HER2 directed therapies have dramatically altered survival outcomes for patients treated in the neoadjuvant and adjuvant setting[1,2]. Preoperative chemotherapy has been typically used for locally advanced breast cancers with the aim of treating micrometastases early and downstaging tumours to permit breast conservation surgery. Its role in patients with HER2 positive breast cancer has been substantiated in several clinical trials.

A large amount of pre-clinical and clinical data produced over the last decade have made it evident that immune biology associated with solid tumours, as well as individual immune genetic traits, contributes to survival. An increasing emphasis has been out on the importance of tumour microenvironment and the complex interplay between neoplastic cells and the host's immune system. Cancer-associated inflammation produces myeloid-derived suppressor cells. Inflammatory cells have been shown to promote tumour cell proliferation, angiogenesis, invasion and metastatic dissemination. Host systemic markers of inflammation, including C-reactive protein (CRP) and the neutrophil to lymphocyte ratio (NLR) are associated with a poor prognosis in solid tumours.

NLR reflects the myeloid and lymphocytic lineages in peripheral blood and is a sensitive marker of altered myelopoiesis arising in cancer. Lymphocytes suppress cancer progression and lymphopenia is an independent predictor of inferior survival. Studies show that the presence of tumour-infiltrating lymphocytes are associated with better responses to therapy[3,4]. NLR plays an important prognostic role in solid tumours. Higher NLR is significantly associated with reduced overall survival, reduced cancer-specific survival, and reduced progression-free and disease-free survival in a variety of cancers and stages of disease It has also been shown to be predictive the neoadjuvant setting, as well as amongst phase 1 clinical trial patients [5].

Pre-operative NLR significant is associated with recurrence-free survival[5]. Chemotherapy can normalize elevated NLR early after the introduction of treatment and early changes in NLR are associated with response to therapies [6,7]. NLR represents a potential area for tailoring of therapy in patients with advanced cancer. It could allow early adaptation and discontinuation of ineffective treatment which would minimise toxicity and may improve the quality of life of cancer patients [8].

PLR is calculated as platelet counts divided by lymphocyte counts. Increasing evidence shows that PLR can be used as a prognostic and predictive biomarker in patients with breast cancer and may be helpful in-patient selection. Meta-analysis has now confirmed that high baseline PLR is indicative r of poor prognosis in patients with breast cancer [9].

Methods

We conducted a retrospective analysis on a prospectively maintained database – called the *One Thousand HER2 Patients Project* – of all patients with HER2-positive breast cancer treated with trastuzumab at the Department of Medical Oncology of St Vincent's University and St Vincent's Private Hospitals in Dublin, Ireland.

This database was established in 2010 with the aim to create a clinical resource for translational studies across all the different stages of HER2-positive breast cancer.

To be included in the present study, patients must have Stage I to III invasive breast cancer which was HER2-positive in accordance to the international guidelines (i.e. ASCO/CAP guidelines) in use at the time of diagnosis, must have received at least one dose of trastuzumab-containing therapy, and have adequate follow up information. Also, full details on tumour biology (i.e. tumour grade, oestrogen [ER] and/or progesterone receptors [PgR]), as well as information on all pharmacological therapies administered (i.e. dates, schedules and doses of all cycles of treatments) had to be available for review. Patients diagnosed and followed up at our Institution but who received treatments, even only in part, elsewhere were excluded.

For all patients, we recorded the dates of initial diagnosis of breast cancer (based on the first Pathology report showing invasive carcinoma), of definitive breast surgery, of the first and last administration of trastuzumab, and last follow up at our Institution or death. Most patients had a fine-needle aspiration (FNA) for cytological examination in case of abnormal axillary lymph nodes on imaging. Patients with unequivocal metastatic involvement of supraclavicular or internal mammary lymph nodes (Stage N3b and N3c) – confirmed by either FNA/core biopsy or PET-CT – and those who had inoperable locally advanced breast cancer were excluded from this study. The clinical and pathological data of all patients deemed eligible for the study were individually reviewed and verified against the patients' hospital medical records as the main source document. In order to ensure that most patients had a minimum of three years of follow up, we included in the study only patients who were receiving neo-adjuvant chemotherapy and were treated in St Vincent's University Hospital between March 2006 –July 2016. For those patients who relapsed after curative therapy, we recorded the date and the site of relapse (loco-regional or distant). The database was locked for outcome analyses on March 31st, 2017.

The primary objective of this study was to analyse the possible correlation between NLR and PLR with disease free survival (DFS) and overall survival (OS) in patients with locally advanced operable HER2-positive breast cancer treated with neo-adjuvant chemotherapy. Patients were eligible if they had locally advanced HER-2 positive breast cancer, were receiving neo-adjuvant chemotherapy and were treated in St Vincent's University Hospital between March 2006 –July 2016 Retrospective data collection captured NLR and PLR at baseline, defined as the closest full blood cell count (FBC) available to the date of the initiation of neo-adjuvant chemotherapy. The survival benefit of NLR and PLR at baseline with respect to overall survival (OS) and progression free survival (PFS) were examined with Kaplan Meier curves with log-rank testing. The prognostic value of NLR and PLR were examined with univariate analyses using the cox proportional hazard regression model for hazard ratio (HR) with respect to OS and DFS.

Results

One-hundred-fifty-six patients were identified in the database who met all the pre-defined inclusion/exclusion criteria outlined above. Patients had a median age of 55.6 years (range: 27-78 years). Median time from initial diagnosis to HER-2 therapy was 4 weeks (range: 1-18 weeks).

In terms of tumour characteristics; majority of patients (99 pts, 63%) had grade 3 histology, were oestrogen receptor (ER) positive 93 (60%) patients and were lymph node negative in 111 (71%) patients. TCH chemotherapy was administered to 116(74%) patients, while 20 (13%) patients received ACTH/FEC and TH. Full patients' characteristics are detailed in Table 1. Median follow up was 4.3 years (1.2-10.9 years)

In terms of peri-operative characteristics, the median time from diagnosis to surgery was 24 weeks. The rate of pathological complete response was 64 (41%). Median DFS and OS were not reached for all analyses. DFS rate 92% and OS rate is 96%. Baseline NLR < 2.5 was significantly associated with improved DFS (p= 0.02) and OS (p=0.04) (Figure 1 and Figure2). Baseline PLR <150 showed a statistically insignificant trend towards improved DFS (p= 0.61) (Figure3), however baseline PLR<150 demonstrated a statistically significant improvement in OS (p= 0.04) (Figure4). On univariate analyses for OS showed HR 0.13 (p=0.06) and HR 0.14 (p=0.07) for NLR<2.5 and PLR<150 respectively, and for DFS showed HR 0.34 (p=0.05) and HR 0.30 (p=0.04) for NLR<2.5 and PLR<150 respectively.

Figure 1: Baseline NLR and Disease-Free Survival.

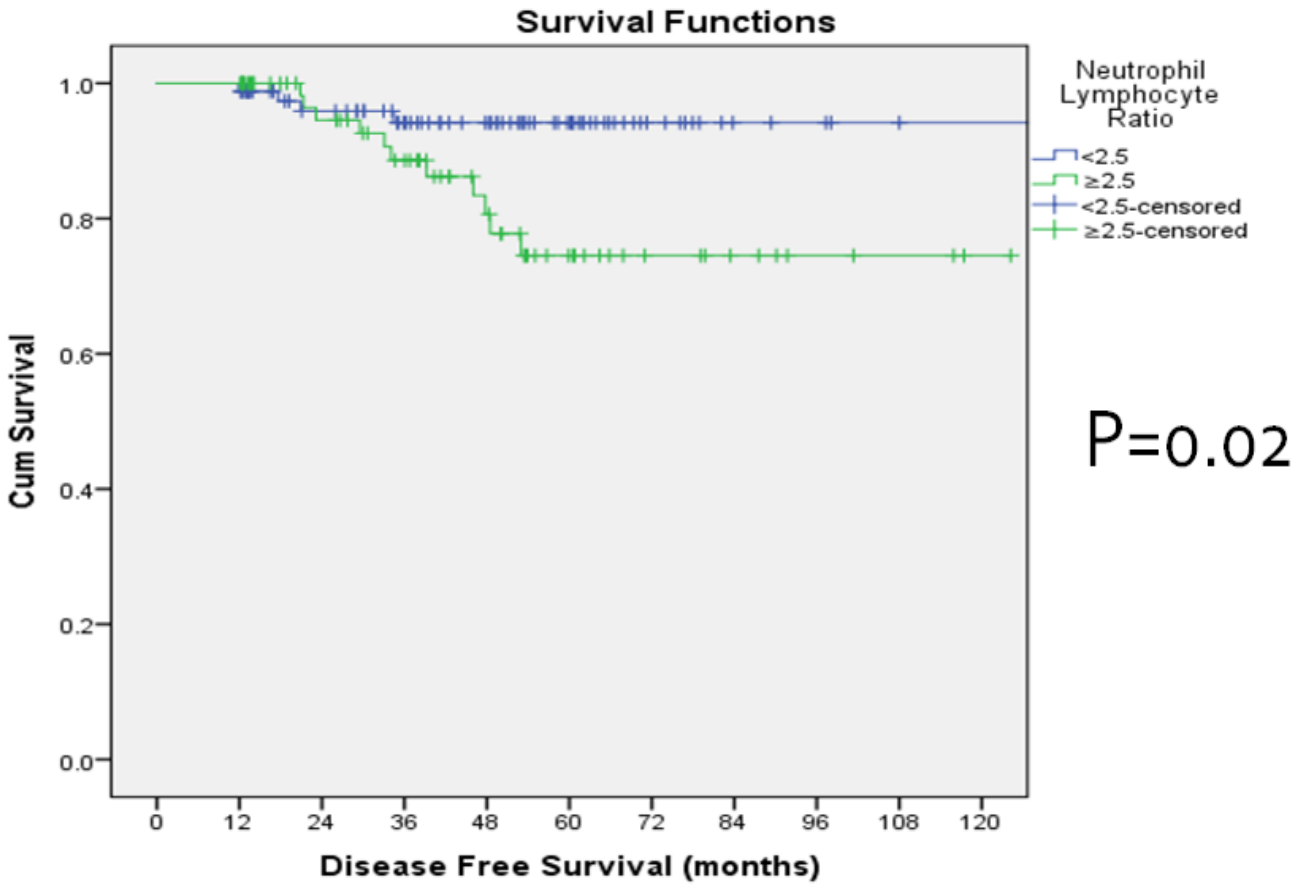


Figure 2: Baseline NLR and Overall Survival.

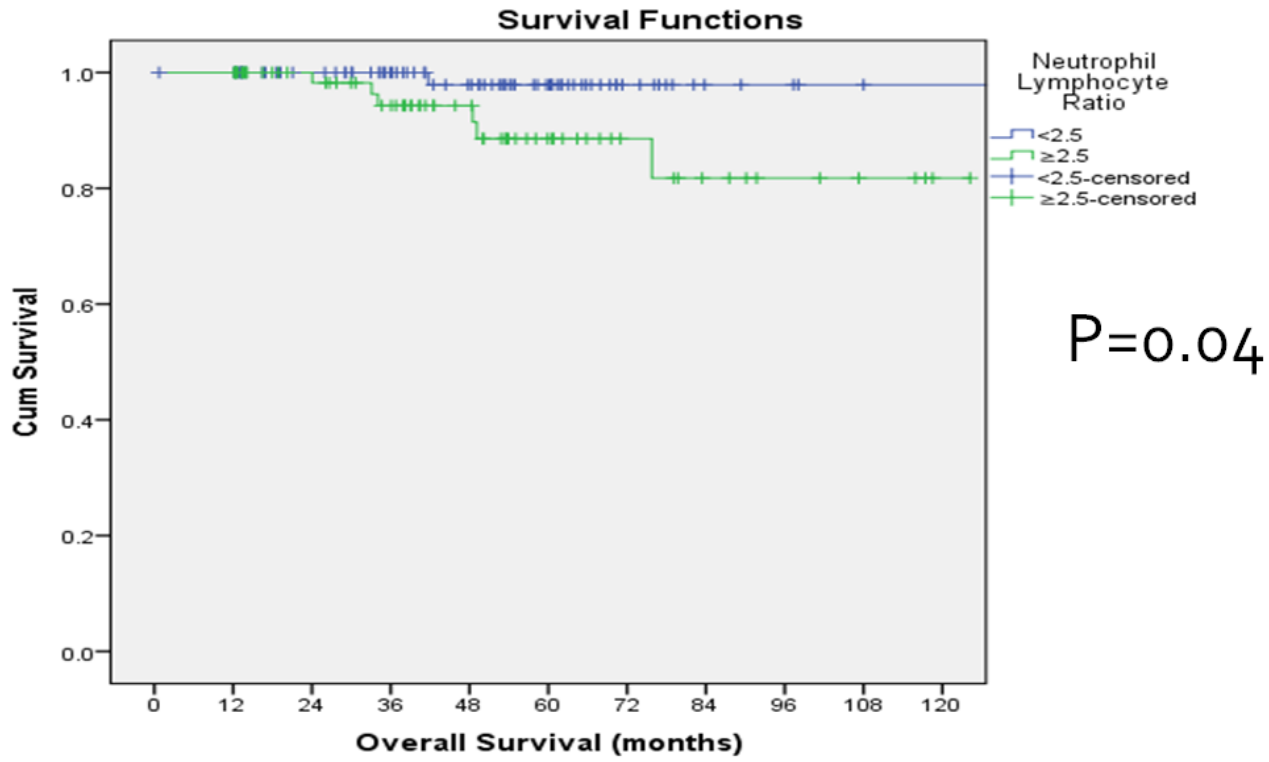


Figure 3: Baseline PLR and Disease-Free Survival.

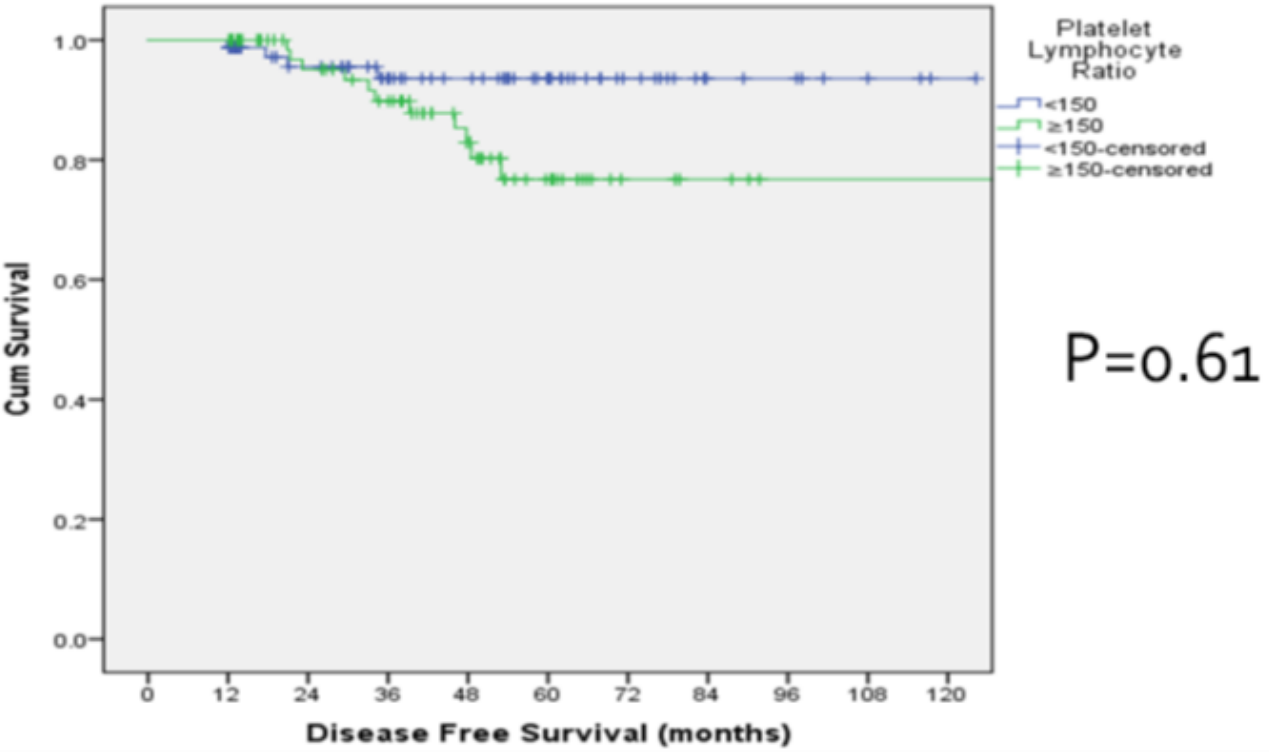
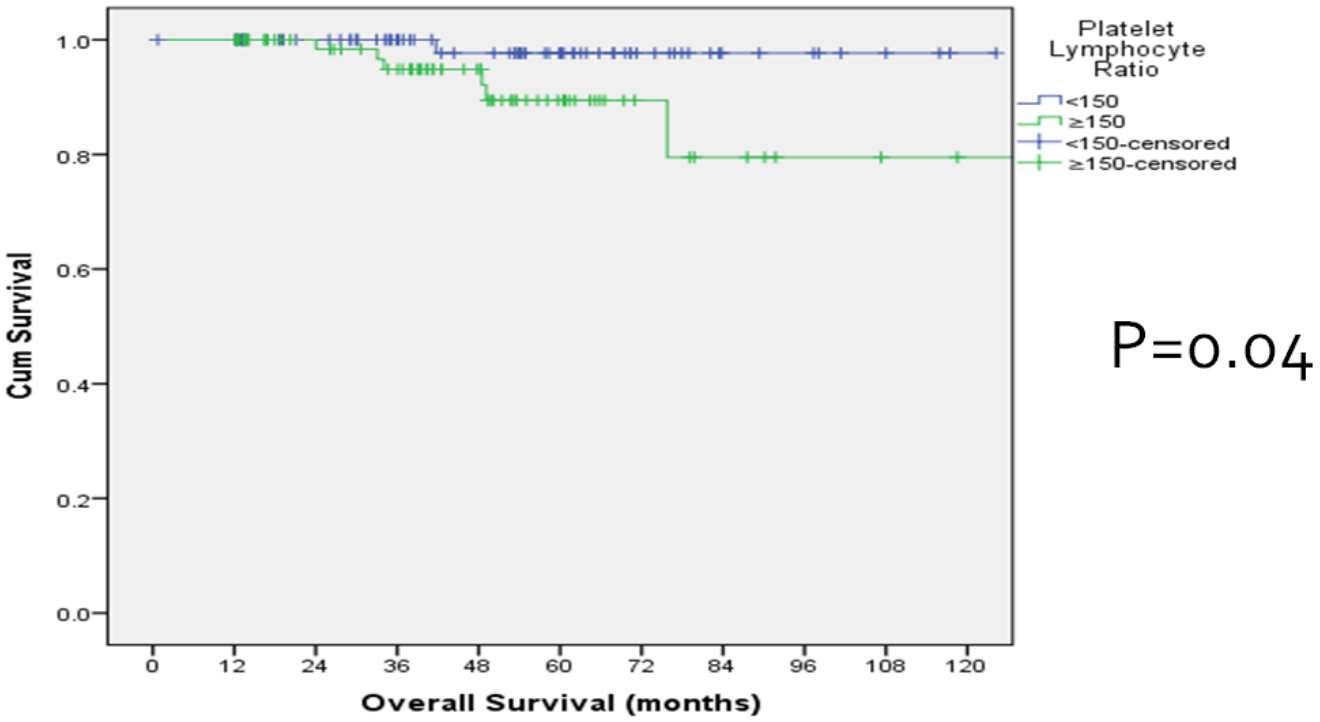


Figure 4: Baseline PLR and Overall Survival.



Discussion

Several studies have shown that elevated NLR is associated with worse survival in patients with various metastatic solid tumours, irrespective of the primary tumour site, line of chemotherapy, age, gender and ECOG [8]. NLR has prognostic value as a continuous variable with research showing that an increase in NLR of 1 standard deviation (SD) increased the risk of death by 35% ($p<0.0001$) in solid tumours [10].

Pre-operative NLR is significantly associated with recurrence-free survival in solid tumours[11]. Chemotherapy can normalize elevated NLR early after the introduction of treatment and early changes in NLR are associated with response to therapies[4,11]. NLR represents a potential area for tailoring of therapy in patients with advanced cancer. It could allow early adaptation and discontinuation of ineffective treatment which would minimise toxicity and may improve the quality of life of cancer patients [8].

NLR appears to be a useful tool in patients receiving immunotherapy. High NLR at baseline and during treatment is adversely prognostic in patients with advanced solid tumours receiving PD-1/PD-L1 inhibitors whilst decreasing NLR over time is associated with response to immunotherapy. NLR and PLR may be useful in for selection of patients and could be considered in the baseline evaluation of candidates for immunotherapy. NLR is not helpful in predicting risk of immune toxicity. However, as immune related adverse events (irAEs) can be life-threatening and treatment-limiting, appropriate and timely identification of patients not responding to treatment would avoid toxicity and minimise unnecessary exposure to therapy unlikely to be effective [12, 13]. All prospective studies of immunotherapy in solid tumours could consider the inclusion of baseline and serial NLR data.

Our results show that a pre-treatment NLR >2.5 and PLR > 150 are adverse prognostic factors in locally advanced, operable HER2-positive breast cancer patients receiving anti-HER2 containing neoadjuvant chemotherapy. Previous studies of NLR in breast cancer demonstrate that NLR has a significant prognostic effect on OS and DFS both in early and advanced disease. The magnitude of effect on DFS is highest in ER-negative, HER2-negative subtypes. It is clear that different clinical outcomes are seen amongst patients with similar classical prognostic factors and the role of inflammatory cells and mediators in the tumour microenvironment in cancer progression may account for some of this variability.

In the future improvement in technology could allow improved understanding of this area. Immunomethylomics is a technique that allows complete characterization of patient immune profiles, using DNA from archival peripheral blood after application of methylation profiling. This technique could explore aberrant immune profiles in the context of cancer-associated inflammation, potentially adding significantly to prognostic and mechanistic information for solid tumours [14].

NLR and PLR are inexpensive and readily available prognostic markers that could be incorporated into clinical tools to prognosticate patient outcomes after systemic therapy. Serial NLR and PLR may be useful for early tailored treatment adjustments as well for treatment selection and de-escalation.

In conclusion, our single-institution study in a homogenous cohort of patients with HER2-positive operable breast cancer treated with neo-adjuvant anti-HER2-containing chemotherapy demonstrates that NLR and PLR at baseline can be a useful predictor of long-term prognosis. This study represents one of the largest real-world datasets looking at NLR and PLR within this patient cohort. NLR and PLR may have a helpful role to play in the refinement of risk estimates within disease stages and subgroups, treatment de-escalation and for clinical trial stratification.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

Corresponding Author:
Dr Deirdre Kelly
St. Vincent's University Hospital,
Dublin.
E-mail: deirdre.kelly.2108@gmail.com

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