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Comment on 'Existing prognostic models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma'

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Sir,

We feel compelled to comment on the article of Meniawy *et al* (2013) to provide perspective on the value of the neutrophil to lymphocyte ratio (NLR) as a prognostic indicator in patients with malignant pleural mesothelioma (MPM). The Western Australia-based authors of this article have concluded from their analysis that the NLR did not provide prognostic value, whereas the Cancer and Leukemia Group B (CALGB) and European Organisation for Research and Treatment of Cancer (EORTC) prognostic guides did.

However, there are some flaws in the data that have not been adequately acknowledged and that might have had a major impact on the conclusions. The principal flaw was that although intended to be an analysis of 369 consecutive patients presenting to a single treatment centre, this number was reduced by 95 (26%) based on failure to meet fairly arbitrarily defined inclusion criteria of: availability of a full blood count within 90 days of diagnosis; cytologically or histologically confirmed diagnosis of MPM; absence of concurrent haematological malignancy and duration of follow-up >90 days. A majority of patients (64) were excluded on the basis of missing laboratory data (unspecified as to which). There was no attempt to compare the characteristics of those excluded with those included to determine comparability of populations. In addition, of the remaining 274 patients, 169 (46% of initial) were treated with chemotherapy, whereas 105 (28%) received no systemic chemotherapy. In spite of 28% of patients receiving no treatment at all, the median survival for the entire group was 13.3 months with a median of 15.3 months for the chemotherapy group. These data appear to show unusually good overall survivals and are suggestive of selection bias, possibly caused by the exclusion of the 95 patients. In our original study in consecutive patients receiving systemic chemotherapy for MPM (Kao *et al*, 2010), the median survival was very similar to that reported by Vogelzang *et al* (2003) in their phase III study that compared pemetrexed and cisplatin with cisplatin alone.

The findings of Meniawy and colleagues are also contradictory to the findings of other investigators in regard to the prognostic significance of NLR in MPM and numerous investigators in other tumour types (Cedres *et al*, 2012, 2013; Pinato *et al*, 2012; Guthrie *et al*, 2013; Paramanathan *et al*, 2014); however, the contradictory nature of their own findings was not adequately highlighted or explanation attempted. We have recently presented the outcomes of prognostic factors in a large cohort of patients ($n=913$) based on the clinical and laboratory data extracted from the records of the Dust Diseases Board of New South Wales (NSW), where median survival of patients was 10 months (Linton *et al*, 2013). In this large population-based study including $>90\%$ of the NSW patients seeking compensation from 2002 to 2009, NLR>5 was again found to be an independent poor prognostic factor (HR$=1.21$; CI: 1.02–1.44; $P=0.03$) in multivariate analysis (624 patients in the model), along with non-epithelial histology, age >70 years, male gender, stage III/IV, platelet count $\geqslant 400$, haemoglobin $>1\,\mathrm{g\,dl^{-1}}$ decrease, negative calretinin staining in tumour specimen, not receiving pemetrexed chemotherapy and not receiving extrapleural pneumonectomy (EPP). Although the clinical factors were not in the final multivariate model, performance status was indirectly assessed in the model by including patients who received chemotherapy and EPP.

In addition, we felt that the interesting observation of the significant predictive value of normalisation of NLR after one cycle of chemotherapy was brushed over in the article. This confirmatory finding after our initial article (Kao *et al*, 2010), along with the recent study demonstrating normalisation of NLR (<5) predicting for a survival benefit of 7 months in a series of 118 patients participating in phase I trials (Pinato *et al*, 2014), suggests that prospective validation of NLR is warranted.

Finally, there appears to be a misconception that we were seeking a universal prognostic marker that could guide treatment outcomes for all. The series investigated by us confirm that determination of the NLR is a relatively simple way to assess prognosis in certain groups of patients with MPM; however, (ongoing) prospective validation will teach us how to properly use this parameter in clinical practice.

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