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Comment on 'A meta-analysis of CXCL12 expression for cancer prognosis'

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Sir,

The current letter refers to the meta-analysis by Samarendra *et al* (2017) on the prognostic relevance of CXCL12 (SDF1) expression for cancer progression, as was recently published in the *British Journal of Cancer*. The authors summarised a total of 38 cohorts and observed that cancer patients with high expression of CXCL12 conferred a reduced overall survival (OS) (hazard ratio 1.39, 95% CI 1.17–1.65), but not recurrence-free survival (RFS) (hazard ratio 1.12, 95% CI 0.82–1.53). They claimed that determination of CXCL12 expression could potentially serve as a prognostic cancer biomarker in various human cancers. This is an interesting and clinically valuable study, however, we would like to address a few concerns on the methodology and the interpretation of the findings of this study.

Literature searching concerns. By replicating the literature search and tracking the contents of the eligible studies, we noticed that they seem to have missed some potentially important articles satisfying the inclusion criteria (Saigusa *et al*, 2010; Yu *et al*, 2016). We would like to cautiously clarify that those missing articles from the relevant literature contained survival data indispensable for considering the issue on the prognostic value of CXCL12 expression.

Methodological concerns. Significant heterogeneity among the studies cannot draw firm inferences, which originates from a statistical or clinical aspect. Though the authors tried to diminish the statistical heterogeneity through a random effects model, between-study heterogeneity was still prominent for both OS ($I^2 = 86\%$) and RFS ($I^2 = 85\%$) subsets. Meta-regression could have been performed to better clarify the exposure interactions with study-level factors for meta-analyses with a larger number of studies (generally > 10) (Schmid *et al*, 2004). In this meta-analysis, there was a sufficient number of studies for both OS and RFS subsets. We thus consider it might be more appropriate to perform meta-regression instead of subgroup analysis.

On account of the clinical inter-study heterogeneity, besides the mentioned attributing factors such as cancer type, study design, sample size and method for defining CXCL12 expression cutoff, we believe that more study-level factors should be investigated including patient baseline characteristics (age, body mass index, disease stage, and so on), molecular profiles (tumour-infiltrating inflammation, *KRAS, BRAF* and *PIK3CA* mutation status) (Mei *et al*, 2014, 2016), study quality, patient follow-up duration and statistical method (adjusted variables for survival analysis).

Concerns about specific points. We consider the selection of the main study end points improper. As RFS or cancer-specific survival is defined as the time from patient enrolment to disease recurrence or death from specific cancer, RFS could have been chosen as the main outcome with a relatively good number of studies. OS, however, though commonly used, is defined as the time from patient enrolment to death from any cause, and did not distinguish cancer-related death or other causes. Since patients in different studies varied in ages, the reported effect of CXCL12 expression could not reflect its true survival effect well, and could not potentially serve as a good prognostic biomarker based on current evidence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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