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LETTER TO THE EDITOR

WILEY Cancer Science

# Prognostic value of CpG island methylator phenotype in gastric cancer

Dear Editor,

This letter reports some observations on the recent article entitled "Meta-analysis of the prognostic value of CpG island methylator phenotype in gastric cancer" by Powell et al[1] (2018) reporting that gastric cancers showing CpG island methylator phenotype-high (CIMP-H) were associated with poor 5-year survival. The conclusion was reached by a well-conducted meta-analysis. However, as the authors claimed, there was significant heterogeneity among the 10 included studies ($I^2$ = 88%, $P < .001$), but they applied a fixed-effects model, which might limit the conclusion. As a result of a lack of a standardized definition of CIMP in gastric cancer, the authors noticed that the conflicting survival results might be caused by the choice of CIMP gene panel. Currently, gene-specific methylation markers and genomewide DNA methylation profile were the 2 major methods to define CIMP.

To limit the heterogeneity among studies and make the conclusion more precise, we regrouped the 10 included studies into 3 subgroups according to different methodologies and the similarities of gene panels, and then carried out subgroup analysis. The studies of Park et al[2] and Shigeyasu et al[3] were classified as the multiple gene panel group because over 15 CIMP marker genes were used in each of them. An et al,[4] Ben Ayed-Guerfali et al,[5] He et al,[6] Ksiaa et al[7], and Kusano et al[8] were classified as the *p16* or *MINT*-based gene panel group, whereas the remaining 3 studies (Chang et al,[9] Chen et al[10] and Liu et al[11]) were classified as the mixed gene panel group because there were no similarities among them. By subgroup analysis, we found that CIMP-H was significantly associated with poor prognosis in the *p16* or *MINT*-based gene panel group, but not in the other 2 subgroups (Figure 1A). Interestingly, the overall effects of CIMP-H in the *p16* or *MINT*-based gene panel group were almost the same as those in the total of the 3 subgroups ($Z$ = 2.62, $P$ = .009; $Z$ = 2.61, $P$ = .009) and the *p16* or *MINT*-based gene panel group presents 51.5% in weight among the 3 subgroups, suggesting that the overall effects of CIMP-H in the total of the 3 subgroups were mainly decided by the *p16* or *MINT*-based gene panel group.

As a result of large heterogeneity, we then analyzed the data by the random-effects model. Surprisingly, in all 3 subgroups, CIMP-H did not have any association with poor 5-year survival ($P > .05$) (Figure 1B). In summary, we may conclude that CIMP is not a prognostic marker in gastric cancer.

## CONFLICT OF INTEREST

Authors declare no conflicts of interest for this article.

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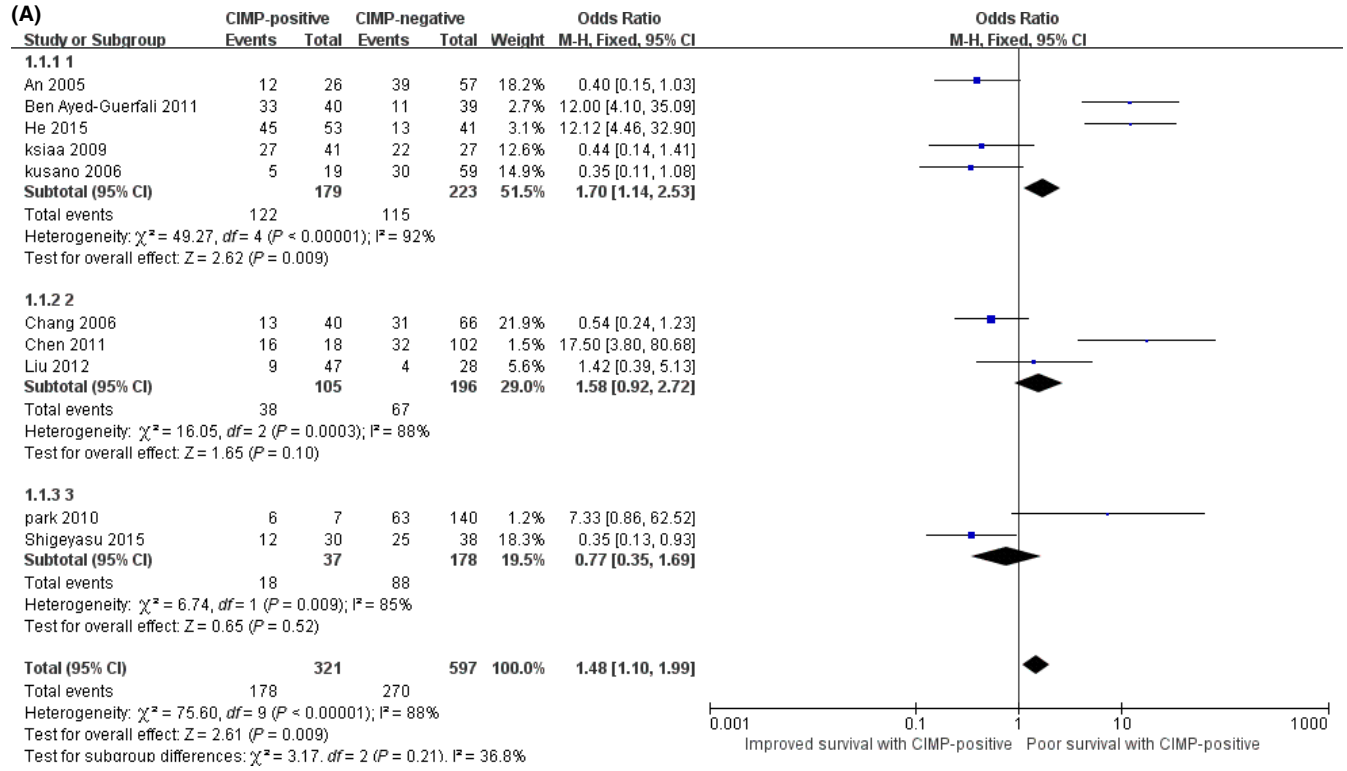


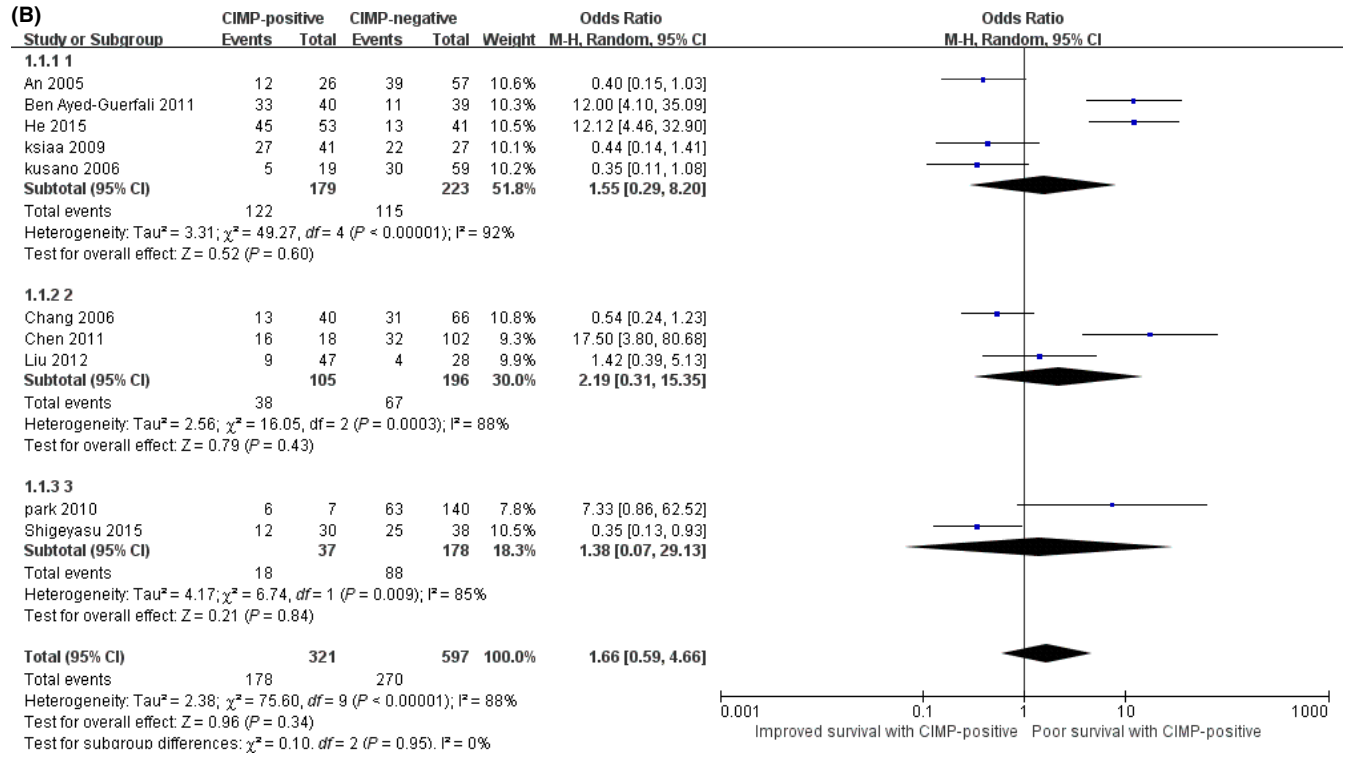


**FIGURE 1** Subgroup analysis of association between CpG island methylator phenotype (CIMP) and 5-y death rates. A, Fixed-effects model was used. B, Random-effects model was used

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