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Original Article

Modified glasgow prognostic score as a prognostic factor in gastriccancer patients: a systematic review and meta-analysis

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Abstract: Objective: Modified Glasgow prognostic score (mGPS) had been reported to associate with the prognosis ofgastric cancer (GC), butits significance in gastric cancer patients has not been studied fully. Methods: PubMed; EMBASE; Web of Science and CNKI data base were searched to identify studies using the mGPS in gastric cancer patients. Outcome measures that were evaluated included overall survival (OS), lymphatic invasion and venous invasion inpatients with gastric cancer. Results: A total of seven studies comprising 3206 patients were included in the meta-analysisof which all used OS as an outcome measure, three studies reported lymphatic invasionand three evaluated venous invasion. The results show that OS was worse in patients with an mGPS=1 and 2 (odds ratio [OR]=2.54, 95% [CI]: 1.62-3.98 and OR=12.02, 95% [CI]: 6.79-21.28, respectively) compared with those with a score of 0 (both $P<0.01$). Furthermore, gastric cancer patients with mGPS≥1 have higher rates of lymphatic and venous invasion with ORs of 2.51 (95% CI: 1.80-3.51) and 2.63 (95% CI: 1.35-5.11) respectively (both $P<0.01$). Conclusions: Them GPS could be used as a prognosis predictorfor gastric cancer patients and associated lymphatic and venous invasion.

Keywords: mGPS, gastric cancer, prognostic factor, meta-analysis

Introduction

Gastric cancer (GC) is the fourth most common cancer andsecond leading cause of cancer-related mortalityin the world [1, 2]. Although surgery and chemotherapy have improved treatment outcome, the survival rate of patients with GCremains unsatisfactory [3]. As treatment plans are becoming more individualized for each patient, it is important to assess disease progression in a timely manner and accuratelyevaluate the prognosis [4, 5]. Tumorin flammatory markers are useful indicatorsof disease development as the inflammatory response is known to promote tumor growth, invasion, angiogenesis and metastasis [6]. Indeed, a close relationship between tumor prognosis and systemic inflammation has been established using markers detected in peripheral blood [7]. Chronic inflammation has also been associated with the progression of GC [8-10], though the exact mechanism for this requires further study.

The modified Glasgow Prognostic Scores (mGPS) provides an inflammation-based prognostic assessment of various tumor type [11, 12]. Despite some studies that have reported the association between mGPS and GC patients, due to differences in inclusion criteriaof GC patients and limited sample sizes limiting its role. Its significance in patients with gastric cancer has not been studied fully. So, it is reasonable to hypothesize that mGPS is a good candidate for predicting the prognosis of GC. In order to more clearly evaluate this, a meta-analysis was conducted to determine whether the mGPS is a useful prognostic factor in GC patients and to assess the relationship between mGPS and clinico pathologic parameters.

Materials and methods

Data sources and searches

The following databases were searched for relevant articles published up until December

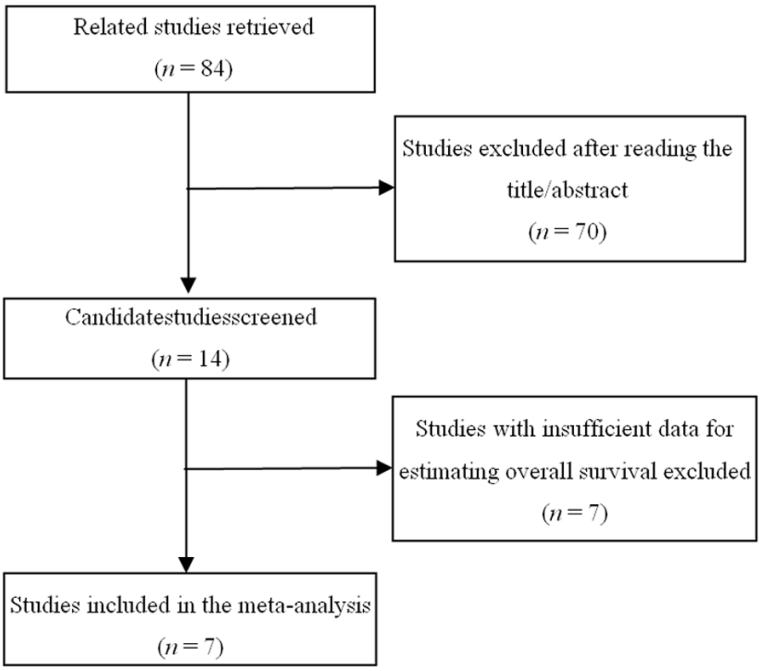

Figure 1. Flow diagram for inclusion of studies included in the meta-analysis.

2014: PubMed; EMBASE; Web of Science and the China National Knowledge Infrastructure. Search terms included "gastriccancer", "prognostic", "mGPS" and "modified Glasgow Prognostic Score". Two reviewers manually search ed the reference lists of identified studies for potential related articles. Only literature published in peer-reviewed journals was included.

Inclusion and exclusion criteria

For inclusion in the meta-analysis, relevant studies were required to include: 1) pathologic examination for diagnosis of GC; 2) pretreatment C-reactive protein (CRP) and albuminlevelsmeasured from peripheral blood samples, mGPS evaluation criteria are formulated by their own laboratories; 3) multivariate analysis for estimation of the hazard ratio (HR). Patients who had other inflammatory diseases causing serum elevations of CRP and albumin were excludedfrom the study. Nonhuman GC studies, duplicatearticles, abstracts and letters were excluded from the analysis. Two reviewers evaluated all candidate literature and resolved any disagreement by discussion.

Data extraction

The following data were extracted from relevant identified: author's first name, year ofpublication, country and size of the population studied, Tumor-node metastasis stage of GC; treatment, the number of patients with mGPS=0, 1 or 2; follow-up period, lymphatic and venous invasion, and overall survival (OS) rate. Some studies do not provide exhaustive OS, we calculate the number of overall survival patients based on overall survivalfigure in the studies.

Statistical analysis

Analysis was conducted using RevMan 5.2 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Associations between mGPS and clinical or pathologic parameters were performed using odds ratios (OR) and 95% confidence intervals (CI). If several estimates were reported with in the same article, the strongest value was selected. The estimates of ORs were weighted and pooled using the Mantel-Haenszelfixe deffects model. If $I^2 \geq 50\%$, the random-effects model was appliedto calculate the pooled OR and 95% CI. Statistical heterogeneity was assessed using the Cochran's Q and I^2 statistics, Publication bias was assessed by visual inspection of the funnel plot. All statistical tests were two-sided, and statistical significance was defined as $P \leq 0.05$.

Results

Study selection

A flow chart depicting the search and study selectionis showed in **Figure 1**. The initial search identified 84 studies, of which seven studiescomprising 3206 patients that were published between 2011 and 2014 were finally included for the meta-analysis [12-18]. Study characteristics are presented in **Table 1**.

OS

There was significant heterogeneity ($I^2 \geq 50\%$) among these studies with regard to mGPS and

Table 1. Baseline characteristics of the studiesincluded in the meta-analysis

Ref.	Study region	Samples (*n*)	Treatment	Outcome	Clinical stage	Survival analysis	Number of mGPS=0/1/2
Tadahiro*et al.*, 2011	Japan	232	Gastrectomy and lymph nodedissection, no neoadjuvant therapy	OS	GC	Multivariate analysis	140/64/28
Jae-Heon*et al*., 2012	Korea	104	Palliative chemotherapy	OS	Advanced GC	Multivariate analysis	58/29/17
Shinsuke*et al*., 2014	Japan	552	Curative gastrectomy with lymphnode dissection, adjuvant chemotherapy	OS	GC	Multivariate analysis	494/24/34
Kotaro *et al*., 2014	Japan	294	Gastrectomy and lymphnode dissection	OS	GC	Multivariate analysis	174/84/36
Aurello*et al*., 2014	Italy	102	Gastrectomy and lymph node dissection	OS	GC	Multivariate analysis	49/25/28
Jiang *et al*., 2012	Japan	1710	Curative or palliative gastrectomy	OS	GC	Multivariate analysis	1565/78/67
Zhang *et al*., 2014	China	212	Curative or palliative gastrectomy, chemotherapy	OS	Stage III-IV GC	Multivariate analysis	136/45/31

GC: gastric cancer; OS: overall survival; DFS: disease-free survival; PFS: progression-free survival.

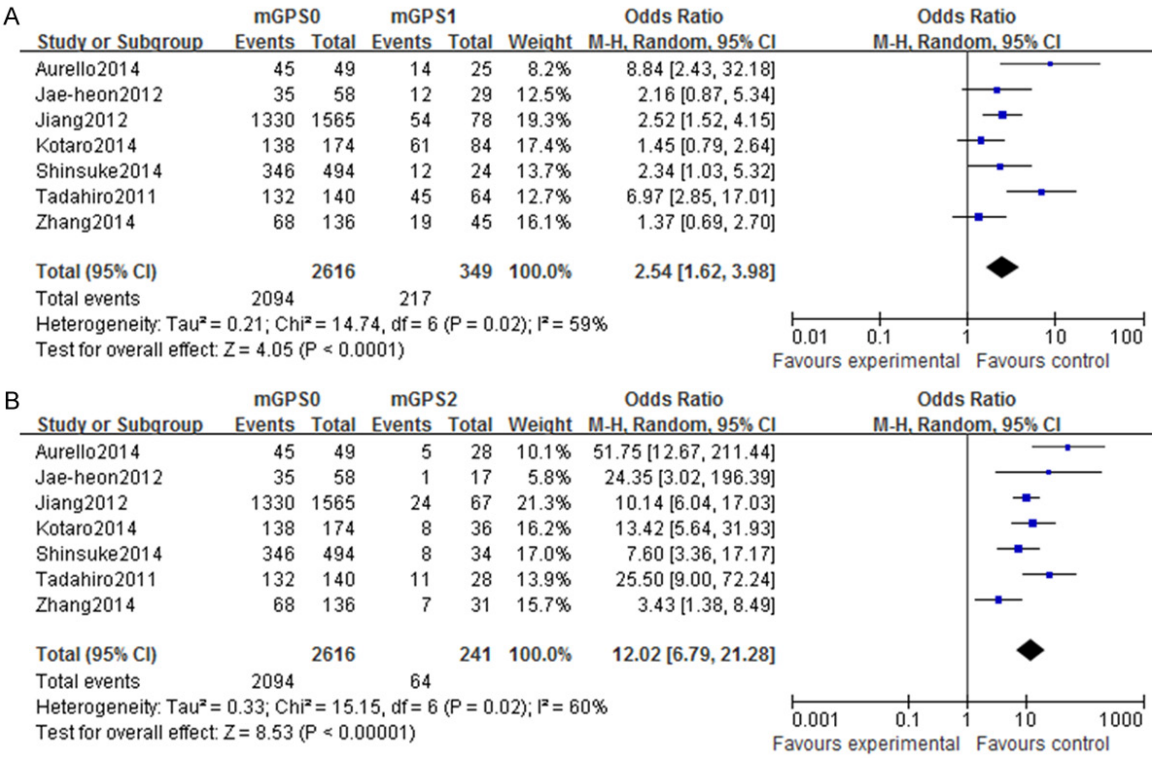

Figure 2. Forest plots of studies evaluating overall survival and modified Glasgow Prognostic Score (mGPS). Overall survival in gastric cancer patients with (A) a mGPS score of 1 and (B) a mGPS score of 2 compared with patients with a mGPS score of 0. CI: confidence interval.

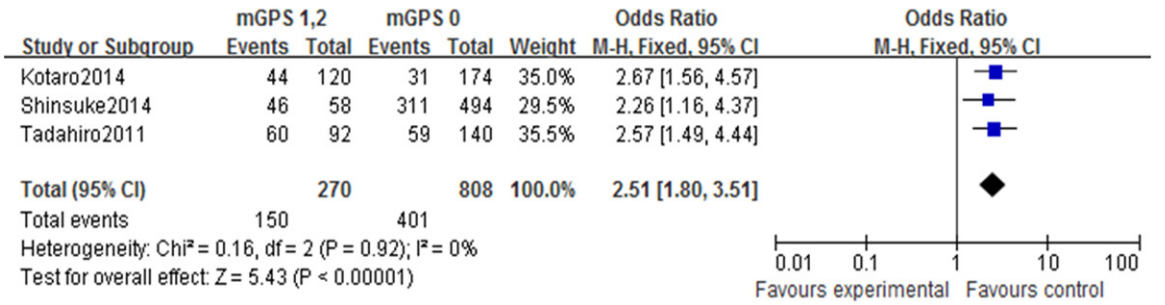

Figure 3. Forest plots of studies evaluating lymphatic invasion and modified Glasgow Prognostic Score (mGPS). Lymphatic invasionin gastric cancer patients with an mGPS score ≥1 compared with patients with a mGPS score of 0. CI: confidence interval.

OS, and thus a random-effects model was applied to calculate the pooled OR and 95% CI (**Figure 2**). The results show that patients with a mGPS=1 or 2 have a shorter OS than those with a score of 0 (both *P*=0.02).

mGPS and lymphatic invasion

Three studies compared mGPS and lymphatic invasion in GC patients. The analysis show thatpatients with an mGPS≥1 havea significantly higher positive lymphatic invasionrate (*P*<0.01) (**Figure 3**).

mGPS and venous invasion

Three studies compared mGPS and venous invasion in GC patients. Arandom-effects model was applied to deal with heterogeneity in this section. The results show that patients with a mGPS≥1 have a significantly higher positivevenous invasion rate (*P*<0.01) (**Figure 4**).

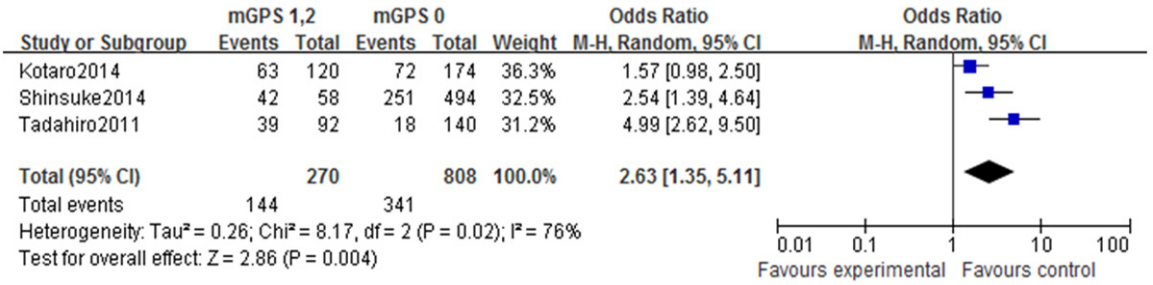

Figure 4. Forest plots of studies evaluating venous invasion and modified Glasgow Prognostic Score (mGPS). Venous invasionin gastric cancer patients with a mGPS score ≥1 compared with patients with a mGPS score of 0. CI: confidence interval.

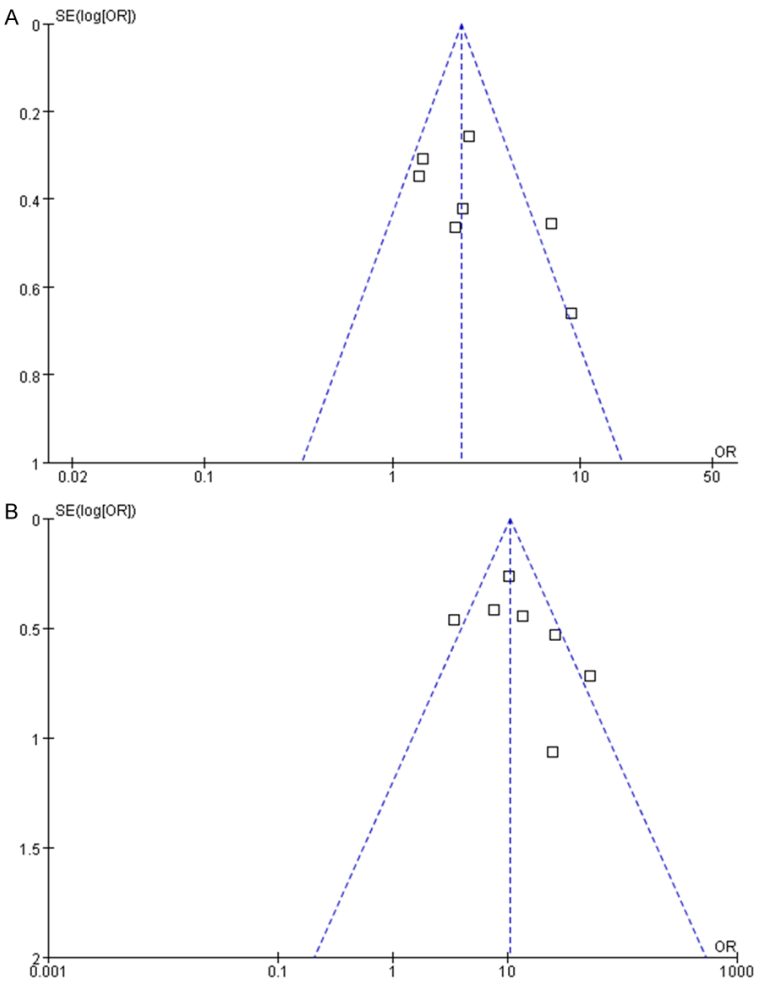

Figure 5. Funnel plot for evaluation OS of publication bias. mGPS 0 and mGPS1 (A) and mGPS 0 and mGPS2 (B). OR: odds ratio.

Publication bias

A funnel plot was used to assess the included studies foroverall publication bias showed symmetry for OS rate (**Figure 5**).

Discussion

Thehost inflammatory response influences the progression of cancerand recent studies indicate that these responses and cancer immune-editing playimportant roles inpromoting the response and immunity of tumors [19-21]. Inflammatory cells provide tumors with nutritional factors, as well as adhesion molecules and chemokines which aid in metastasis [22]. Some inflammatory cytokine increase svascular permeability and promotes tumor metastasis [23].

There are several markers that can be used to assess the systemic inflammatory response, including serum CRP levels and hypoal buminemia. Hypoalbuminemiais thought tobe aconsequence of the inflammatory response associated with elevated CRP levels [24] and has been considered as a prognostic indicator for gastroin testinal tumors [25, 26] colorectal [27, 28], esophageal [29], and pancreaticcancers [30]. The mGPS is basedon evaluation of CRP levels and hypoal buminemia, andhasrecently been associated with the prognosis of patients with digestive tract cancer [31, 32].

Interleukin 1, interleukin 6, tumor necrosis factor and other proin flammatory cytokines can cause serum C-reactive protein elevated in patients with gastric cancer. These cytokines can promote gastric cancer cell proliferation, anti-apoptosis and angiogenesis by activating the downstream transcription factor, such as STAT3 and so on, which is significantly associatedwith inflammation, immunity, and oncogenesis [33, 34] and promotes lymph node metastasis and vascular metastasis [35, 36]. So constitutive activation of STAT3 have a poor prognosisin gastric cancer patients associated with mGPS [37-39]. Thus, mGPS have a close relationship with tumor metastasis in gastric cancer patients. The results of this meta-analysis show that the mGPS can also be used as a prognostic indicator for GC.

In addition to a reduced OS, GC patients with a higher mGPS are more likely to show lymphatic and venous invasion have a worse prognosis. These findings are consistent with previous studies showing thatnode metastasisand angiogenicmetastasis which affect the prognosis of GC [40, 41].

In summary, the results of this meta-analysis indicate that GC patients with a mGPS≥1 have a worse prognosis than patients with a mGPS=0, thus the preoperative mGPS could serve as a prognostic factor to evaluate the survival of these patients. However, the limited number of eligible studiesand different laboratories has different evaluation criteria about mGPSincluded in the meta-analysis necessitates further verification to confirm these results.

Disclosure of conflict of interest

None.

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