

## Review Article

# Prognostic role of modified glasgow prognostic score in patients with cholangiocarcinoma: a meta-analysis and literature review

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**Abstract:** *Background and aim:* Increasing evidence indicates that the modified Glasgow Prognostic Score (mGPS) is a useful biomarker of long-term outcomes in various types of cancer. However, its prognostic value in patients with cholangiocarcinoma is not fully investigated. Thus, we investigated its relationship with overall survival (OS) to evaluate its role in predicting survival in patients with cholangiocarcinoma. *Methods:* PubMed, EMBASE and Web of Science databases were systematically searched to identify studies that evaluated the prognostic impact of the modified Glasgow Prognostic Score (mGPS) in cholangiocarcinoma patients. Meta-analysis using random-effects model was performed to calculate hazard ratio (HR) and corresponding confidence intervals (CIs) respectively. *Results:* A total of five studies comprising 1022 patients were included in the meta-analysis, of which overall survival was used as an outcome measure. The results showed that OS was worse in patients with a mGPS = 1 or 2 with a pooled HR of 1.80 (95% CI = 1.48-2.19,  $P < 0.001$ ) than those with a score of 0. The patients with a mGPS = 0 or 1 have significantly prolonged OS compared with those with a score of 2 with a pooled HR of 3.89 (95% CI = 1.70-8.91,  $P = 0.001$ ). *Conclusions:* The results of this meta-analysis suggest that higher mGPS is associated with poorer survival in patients with cholangiocarcinoma. More well-designed studies are necessary to provide solid data to confirm the prognostic significance of mGPS.

**Keywords:** mGPS, cholangiocarcinoma, survival, meta-analysis

## Introduction

Malignant tumor cholangiocarcinoma (CCA) is a primary tumor arising from the ductal epithelium of the biliary tree. The incidence and mortality rates of cholangiocarcinoma are increasing worldwide, with approximately 5000 CCA-related deaths occurring per year [1]. Curative-intent surgery remains to be the preferred option for all categories of CCA and is shown to give a chance to cure CCA, however, 5-year survival rate of surgical result just ranges from 30% to 41% [2]. The clinical outcomes of CCA remain poor. CCA are often insensitive to chemotherapeutics and resistant to radiotherapy, consequently, limiting the effects of adjuvant chemotherapy and radiotherapy [3].

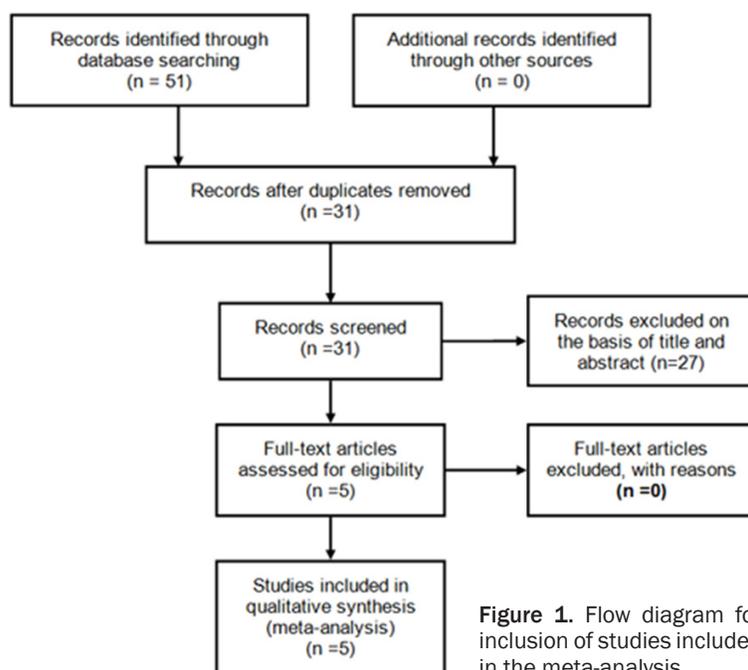
Traditional clinicopathological factors such as the TNM staging system, resection margin, vas-

cular or neural invasion are currently the most important prognostic factors for CCA patients [4, 5]. Treatment plans are becoming more individualized for patients, thus, more clinicopathological factors preoperative or before treatment are essential to assess disease progression and accurately assess the prognosis.

Chronic inflammation has been associated with the progression of CCA, though the exact mechanism for this requires further study. As in various tumor types, the modified Glasgow Prognostic Scores (mGPS) is an independent inflammation-based prognostic factor in cholangiocarcinoma.

Several studies have reported the correlation between mGPS and CCA patients; however, due to the variation in study design and limited sample size, its significance in patients with CCA has not been studied fully [6-8]. Given this, a

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

meta-analysis was conducted to reveal the relationship between mGPS and OS of patients with CCA.

### Methods

#### Search strategy and selection criteria

A comprehensive search was performed in PubMed, EMBASE and Web of Science up to October 29, 2016. The search strategy used both MeSH terms and free-text words to increase sensitivity. The medical subject headings (MeSH) or keywords included “modified Glasgow Prognostic Score”, “mGPS”, “inflammation-based score”, “Bile Duct Neoplasms”, “Cholangiocarcinoma”, “Cholangiocellular Carcinoma”, “Bile duct”, “Carcinoma”, “adenocarcinoma”, “Cancer”, and “Prognosis”.

Two reviewers (ZGT and HZ) manually searched the reference lists of identified studies that appeared to fit the selection criteria. The following inclusion criteria were used: (1) pretreatment C-reactive protein (CRP) and albumin levels was collected; (2) patients were grouped according to the mGPS; (3) relationship between mGPS and cholangiocarcinoma clinicopathological variables or prognosis was displayed; (4) multivariate analysis for estimation of the risk ratio (RR) and 95% confidence interval (CI); The following exclusion criteria were used: (1) letters, editorials, comments, conference abstracts, case reports and review arti-

cles; (2) studies without usable data; (3) studies irrelevant to our topic and duplicate articles.

#### Data extraction

Data was extracted from the eligible studies included in the meta-analysis by two investigators (ZGT and HZ) independently, and disagreements were discussed and reached a consensus by discussion with a third investigator (CJJ). The following relevant parameters were collected: first author, year of publication, country, total patients, treatment methods, gender, follow-up period and survival HR.

#### Statistical analysis

Hazard ratios (HRs) were extracted directly from each individual study. The heterogeneity among studies was evaluated using Chi-square test and  $I^2$  statistics. A  $p$  value  $<0.10$  was considered statistically significant for Chi-square test. For the  $I^2$  statistics, an  $I^2$  value greater than 50% was considered significant heterogeneity among studies. Because of between-study heterogeneity (explored by  $I^2$ ), random effect model was used in this analysis. All statistical tests were two sided, and  $P < 0.05$  was considered statistically significant. The possibility of publication bias was assessed using Begg’s funnel plot and Egger’s tests. All statistical tests were performed using Stata software (version 12.0, Stata Corporation, College Station, TX, USA).

#### Quality assessment

Two reviewers (ZGT and HZ) independently evaluated the selected studies according to Newcastle-Ottawa quality assessment scale. Newcastle-Ottawa Quality Assessment Scale score 6 indicated high quality. Discrepancies were resolved by discussion and consensus.

### Results

#### Study selection and characteristics

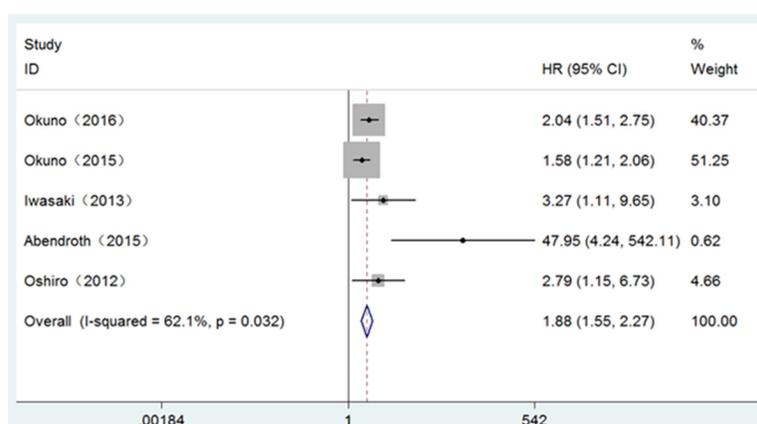
The flowchart of the study selection process is shown in **Figure 1**. The initial literature search yielded a total of 51 studies. After screening

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**Table 1.** Main characteristics of the studies included in the meta-analysis

Study	Year	Country	Cancer Type	Sample Size (M/F)	Treatment	Sample size			HR (95% CI)	Outcome	
						Total	mGPS 0	mGPS 1			mGPS 2
Okuno	2016	Japan	Perihilar cholangiocarcinoma	219 (128/91)	Nonsurgical	219	128	NA	NA	2.04 (1.51-2.75)	OS
Okuno	2015	Japan	Perihilar cholangiocarcinoma	534 (336/198)	Surgical	534	422	NA	NA	1.58 (.21-2.06)	OS
Iwasaki	2013	Japan	Malignant biliary obstruction	60 (32/28)	Nonsurgical	60	36	7	17	3.27 (1.11-9.65)	OS
Abendroth	2015	Germany	Advanced biliary tract cancer	147 (NA)	Nonsurgical	NA	NA	NA	NA	47.95 (4.24-542.11)	OS
Oshiro	2012	Japan	Extrahepatic cholangiocarcinoma	62 (41/21)	Surgical	62	32	OS	6	2.79 (1.15-6.74)	OS

HR: hazard ratios; NA = not available; OS: overall survival; M: male; F: female; NOS: Newcastle-Ottawa-Scale.



**Figure 2.** Meta-analysis of the relationship between elevated modified Glasgow Prognostic Score (mGPS) and overall survival in patients with cholangiocarcinoma. Results are shown as individual and the summary HR and 95% CI.

titles and abstracts, 31 full-text articles were assessed for eligibility. Finally, a total of 5 articles met the inclusion criteria and were included in this meta-analysis. All of 5 articles were retrospective. Among these 5 articles, four are from Japan, one is from Germany. Details of the trials are shown in **Table 1** [6, 8-11].

### mGPS and overall survival

There was significant heterogeneity ( $I^2 \geq 50\%$ ) among 5 studies with regard to mGPS and OS, thus a random effect model was used to calculate the pooled HR and 95% CI (**Figure 2**). The results showed that the prognosis of patients with higher mGPS was poorer than those with lower mGPS. Among these 5 articles, three of them showed that patients with a mGPS = 1 or 2 had a shorter OS than those with a score of 0. The heterogeneity of the data was evaluated by heterogeneity existed among the studies ( $I^2 =$

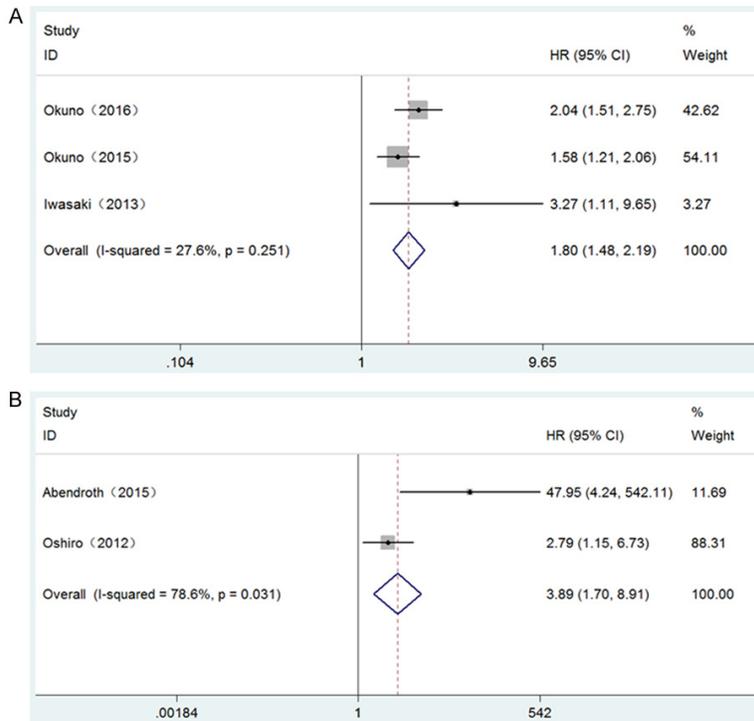
27.6%,  $P = 0.251$ ), and the random-effects model was adopted. Analysis revealed a pooled HR of 1.80 (95% CI 1.48-2.19,  $P < 0.001$ ) (**Figure 3A**). One study explored Glasgow Prognostic Score (GPS) groups of postoperative outcome in patients with extrahepatic cholangiocarcinoma. The mGPS was calculated as follows: patients with both an elevated C-reactive protein (CRP) level ( $>1.0$  mg/dl) and hypoalbuminemia ( $<3.5$  g/dl) were allocated a score of 2. Patients with only an elevated CRP level were allocated a score of 1, and patients with-

out an elevated CRP level were allocated a score of 0. In the same way, GPS2 was also defined as follows: an elevated C-reactive protein (CRP) level ( $>1.0$  mg/dl) and hypoalbuminemia ( $<3.5$  g/dl). Thus, two included studies reveal the result that mGPS0 group and mGPS1 group had a significantly prolonged OS compared with mGPS 2 group or GPS 2 group. The heterogeneity of the data was evaluated by heterogeneity existed among the studies ( $I^2 = 78.4\%$ ,  $P = 0.031$ ), the random-effects model was adopted. Analysis revealed a pooled HR of 3.89 (95% CI 1.70-8.91,  $P = 0.001$ ) (**Figure 3B**).

### Assessment of publication bias

Due to the less number of studies included in our study, we did not draft funnel plot to reveal publication bias.

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**Figure 3.** Forest plots of studies evaluating overall survival and modified Glasgow Prognostic Score (mGPS). Overall survival in cholangiocarcinoma patients with (A) a mGPS score of 0 compared with patients with a mGPS score of 1 or 2 and (B) a mGPS score of 2 compared with patients with a mGPS score of 0 or 1. CI: confidence interval.

### Discussion

The meta-analysis conducted in the present study on 5 studies with a total of 1022 patients with CCA showed that a higher mGPS predicts poorer survival than those with lower mGPS. Similarly, 2 recent meta-analyses revealed the prognostic value of mGPS for gastric cancer and hepatocellular carcinoma respectively [12]. To our knowledge, this is the first meta-analysis assessing the prognostic role of mGPS in CCA.

Inflammation plays an important role in tumor occurrence and development, including matrix degradation, cancer progression, angiogenesis and immunosuppression [13]. For cholangiocarcinoma, the release of inflammatory cytokines and cell death increase cell proliferation, as well as changes in the liver in fibrosis favour tumorigenesis [3]. The mGPS, which involves a selective combination of CRP and albumin levels, has recently proved to be a promising prognostic indicator in patients with various cancers. C-reactive protein, an acute-phase reactant, is synthesized in hepatocytes and in

response to release of cytokines, such as interleukin 1 (IL-1) and interleukin 6 (IL-6) release by immune cells under infection, tissue necrosis, and inflammatory disease [14]. The cytokine interleukin 6 has been proved to be an integral role in cholangiocarcinoma and other cancers as a growth and survival factor, and IL-6 can enhance tumor growth in cholangiocarcinoma by altering gene expression via autocrine mechanisms [15-17].

The CRP acts on tumor cells, leading to tumor cell lysis and tumor progression. The elevated CRP is related to impaired T lymphocytic response within the cancer [18]. Recently, some studies indicated that elevated CRP is an independent predictor of a poor prognostic outcome in cholangiocarcinoma patients [19-21]. Serum albumin is

synthesized by the liver and is the main serum protein. Serum albumin is related to malnutrition and hypoalbuminemia is correlated with cachexia. Thus, albumin is an important marker for evaluating nutritional status in patients with malignancy. Besides, several studies have indicated that the inflammatory response can affect the serum albumin levels [22]. Cancer patients appear to be malnutrition because of the adverse effects imposed by the tumors on the digestive system.

The combination of CRP with serum albumin can improve predictive ability for the survival and individualized therapy of patients with advanced cancers [23]. Hiroki Ishihara et al. have revealed that modified Glasgow Prognostic Score can predict outcomes among patients with metastatic renal cell carcinoma who are receiving first-line sunitinib treatment [24]. Similar results were obtained for mGPS in meta-analysis, mGPS is an independent prognostic factor for hepatocellular carcinoma [12] and gastric cancer [25]. A study of Imaoka et al. also indicated that the prognostic value of the

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mGPS in patients with pancreatic cancer [26]. Furthermore, pretreatment mGPS is an independent prognostic factor and can be used to predict survival in patients with squamous cell carcinoma undergoing chemoradiotherapy [27]. The results of this meta-analysis show that higher pretreatment mGPS is associated with poorer survival in patients with cholangiocarcinoma.

Nevertheless, there are several limitations in current study. First, the comparison between mGPS1 and mGPS2 was not performed, because the data was not reported in the included studies. Second, different therapeutic measures in this study also inevitably increased the heterogeneity and interfered with the results of the combined analysis. Third, a selection bias was impossible to be avoided because all studies included in this meta-analysis were retrospective. Fourth, a publication bias existed since small-scale studies may remain unpublished and could account for language limitations in the inclusion criterion, consequently, reducing the reliability of interpreting the results.

In conclusion, as an easily measurable significant prognostic factor, mGPS can be a promising prognostic indicator for CCA. Large scale prospective studies that use mGPS as a stratification factor are warranted to confirm our findings.

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### Disclosure of conflict of interest

None.

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