Original Article

Baseline serum lactate dehydrogenase level predicts survival benefit in patients with metastatic colorectal cancer receiving bevacizumab as first-line chemotherapy: a systematic review and meta-analysis of 7 studies and 1,219 patients

Wanjing Feng[1,2#], Yue Wang[2,3#], Xiaodong Zhu[1,2]

[1]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China; [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China; [3]Department of Urology, Fudan University Shanghai Cancer Center, Shanghai 200032, China

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[#]These authors contributed equally to this work.

Correspondence to: Xiaodong Zhu. Department of Oncology, Shanghai Medical College, Fudan University, 270 Dong' An Road, Shanghai 200032, China. Email: xddr001@163.com.

Background: Bevacizumab, a humanized monoclonal antibody against vascular epithelial growth factor, plays a significant role in first-line, second-line, beyond-progression, and maintenance treatment of patients with metastatic colorectal carcinoma (mCRC). Nevertheless, there are currently no biomarkers available to predict patient response or resistance to bevacizumab, which would be useful in clinical trials.

Methods: Using PRISMA guidelines, we conducted a systematic review and meta-analysis of the association between serum lactate dehydrogenase (LDH) level and progression-free survival (PFS), overall survival (OS), and objective response rate in mCRC patients treated with bevacizumab-based first-line chemotherapy. A comprehensive, computerized literature search of PubMed, the Web of Science, Scopus, Ovid, and the gray literature was performed. Only studies conforming to specific eligibility criteria were included. Pooled hazard ratios (HRs) were estimated using random-effects or fixed-effects models according to heterogeneity between studies. Sensitivity analysis was conducted to evaluate the stability of the results by removing each individual study from the meta-analysis.

Results: Seven eligible studies of 1,219 total patients were included in the analysis. Meta-analysis of all studies revealed that high serum LDH level is associated with shorter PFS (HR: 1.43, 95% CI: 1.05–1.94; P=0.023) and OS (HR: 1.667, 95% CI: 1.230–2.259; P=0.001) times in mCRC patients treated with bevacizumab-based first-line chemotherapy. However, there was no significant association between serum LDH and objective response rate.

Conclusions: High serum LDH level is significantly associated with shorter PFS and OS time and may have utility as a prognostic factor for mCRC patients receiving bevacizumab as first-line chemotherapy and as a predictive factor for those receiving bevacizumab-based therapy at other times.

Keywords: Lactate dehydrogenase (LDH); colorectal cancer; bevacizumab

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Introduction

Bevacizumab is a humanized anti-vascular endothelial growth factor A (anti-VEGF) monoclonal antibody that is frequently employed as first-line therapy for patients with metastatic colorectal carcinoma (mCRC) (1). In addition, phase III randomized clinical trials have confirmed the efficacy of bevacizumab as second-line, beyond-progression, and maintenance treatments in this patient population (2,3). However, at present, no biomarkers exist that can predict either the response or resistance to bevacizumab therapy. There is thus an urgent need to identify such predictive biomarkers to enable identification of subjects most likely to benefit from bevacizumab.

Recently, several studies have reported that a high serum lactate dehydrogenase (LDH) level is associated with poor prognosis in patients with CRC (4) and other tumors (5,6). LDH has been identified as a potential signaling molecule for angiogenesis, suggesting a potential mechanistic link between LDH levels and prognosis. High LDH levels inhibit the formation of 2-oxoglutarate, which leads to stabilization of the transcription factor hypoxia-inducible factor α and, subsequently, to increased expression of its target gene vascular endothelial growth factor (VEGF) (7). Azuma *et al.* also demonstrated that patients with high serum LDH levels have increased intratumoral expression of *VEGFA* and *VEGF1* genes (8).

Two retrospective studies have explored a potential predictive role for serum LDH in anti-angiogenic therapy of mCRC patients. Both studies found a significant association between high serum LDH level and poor outcome and response rate (RR) in patients treated with bevacizumab-based first-line chemotherapy (9,10). However, a recent prospective phase II clinical trial (CENTRAL) of a similarly treated mCRC patient cohort confirmed a significant relationship between serum LDH level and overall survival (OS), but not RR (11).

Thus, the association between serum LDH level, outcome, and RR of mCRC patients treated with bevacizumab-based first-line chemotherapy is controversial, and a large prospective study will be required to resolve this issue. In the mean time, we report here the results of a meta-analysis conducted to evaluate the prognostic and predictive role of LDH in mCRC patients treated with bevacizumab-based first-line chemotherapy.

Methods

The systematic review and meta-analysis were conducted according to PRISMA criteria. We performed a comprehensive, computerized search of PubMed, the Web of Science, Scopus, Ovid, and the gray literature for publications up to December 31st, 2018, using the search terms "colorectal cancer", "colorectal carcinoma", "colorectal neoplasm", "lactate dehydrogenase", and "bevacizumab". In addition, reference lists in the identified primary papers and review articles were searched. Eligibility criteria for inclusion in this meta-analysis were: (I) the study evaluated correlations between serum LDH level and survival in mCRC patients receiving bevacizumab-based first-line therapy, (II) the study provided sufficient information for estimation of hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), and (III) the study was published in English. Reviews and studies using animals or cell lines were excluded. Study quality was assessed using the Newcastle-Ottawa Scale.

Data extraction and outcomes

To guarantee homogeneity and to prevent subjectivity in the data collection and entry, the studies were independently assessed by two of the authors (Feng and Wang). The following information was independently extracted: first author names, year of publication, study location, sample size, median/mean age, stage of disease, cut-off value of serum LDH concentration, adjuvant chemotherapy, and survival outcome (*Table 1*).

Statistical analysis

Heterogeneity between studies was assessed by the I^2 statistic and Q test, with I^2>57% or P<0.05, respectively, being considered statistically significant. The extracted HRs were then assessed using a fixed-effects model or, if heterogeneity could not be explained by the fixed-effects model, a random-effects model was applied. In this study, heterogeneity between studies was not significant for OS (I^2=25.8%, P=0.232), and a fixed-effects model was therefore used to analyze the relationship between serum LDH level and OS. However, heterogeneity was significant for progression-free survival (PFS; I^2=59.5%, P=0.043) and for clinical tumor response (complete response, partial response, stable disease, progressive disease; I^2=78.4%, P=0.003), and a random-effects model was applied for these analyses. Next, we performed a sensitivity analysis to evaluate the stability of the results by removing each individual study from the meta-analysis. Finally, Begg's

Table 1 Baseline characteristics in concluded studies

Study	Country	Sample size			Median age, years	Tumor stage	Treatment	LDH		Outcome report
		Total	Colon	Rectum				Cut-off	Detection method	
M Jary [2016]	France	177	120	57	NR	mCRC	First-line chemotherapy and bevacizumab	350 U/L	Serum	OS
N Silvestris [2015]	Italy	139	NR	NR	NR	mCRC	First-line chemotherapy and bevacizumab	NR	Serum	ORR, PFS, OS
M Scartozzi [2012]	Italy	82	NR	NR	61	mCRC	First-line chemotherapy and bevacizumab	588 mg/dL	Serum	ORR, PFS, OS
A Passardi [2015]	Italy	176	NR	NR	67	mCRC	First-line chemotherapy and bevacizumab	UNL	Serum	ORR, PFS, OS
B Cetin [2012]	Turkey	170	100	70	NR	mCRC	First-line chemotherapy and bevacizumab	UNL	Serum	OS
R Giampieri [2017]	Italy	81	61	20	65	mCRC	FOLFIRI and bevacizumab	1.2 ULN	Serum	ORR, PFS, OS
E Diaz-Rubio [2012]	US	394	165	229	63	mCRC	XELOX and bevacizumab	ULN	Serum	PFS, OS

mCRC, metastatic colorectal carcinoma; LDH, lactate dehydrogenase; UNL, upper normal limit; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

funnel plot or Egger's linear regression test were used to assess publication bias. All reported P values were two-sided, and P<0.05 was considered statistically significant. All analyses were performed using Stata software version 12.0 (Stata Corp., College Station, TX, USA).

Results

A flowchart of the literature search, study selection, and the results obtained at each step is shown in *Figure 1*. In total, seven studies with a sample size of 1,219 patients were deemed eligible and included in the analysis. The main characteristics of the studies, which were published between 2012 and 2018, are shown in *Table 1*. HRs were obtained for OS and PFS from seven (9-15) and five (9-11,13,15) studies, respectively, whereas data for evaluation of objective RR were obtained from four studies (9,10,13,15). Among the seven studies, two were prospective phase II clinical trials and five were retrospective cohort studies.

A forest plot, showing HRs, 95% CIs, and the weight of each study in the analysis, was constructed to illustrate the correlation between serum LDH level and PFS (*Figure 2*). A random-effects model was applied because the heterogeneity between studies was significant (I^2=59.5%, P=0.043). The overall HR was 1.43 (95% CI: 1.05–1.94, P=0.023). No significant publication bias was detected, as analyzed by Egger's and Begg's tests (P=0.142, *Figure 3*). These results indicate that high serum LDH level is significantly associated with shorter PFS time in mCRC patients treated with bevacizumab-based first-line chemotherapy.

The heterogeneity between studies with respect to OS was not statistically significant (I^2=25.8%, P=0.232) and a fixed-effects model was used to analyze the correlation between serum LDH level and OS. The corresponding forest plot (*Figure 2*) indicates an overall HR of 1.667 (95% CI: 1.230–2.259, P=0.001). Egger's or Begg's tests indicated no significant publication bias (P=0.881, *Figure 3*). These results indicate that high serum LDH level is significantly associated with shorter OS time in mCRC patients treated with bevacizumab-based first-line chemotherapy.

In contrast to OS and PFS, however, objective RR was not significantly associated with serum LDH in our meta-analysis using a random-effects model (HR: 1.651, 95% CI: 0.689–3.957; P=0.261; *Figure 2*). In addition, no significant publication bias was detected by Egger's or Begg's tests

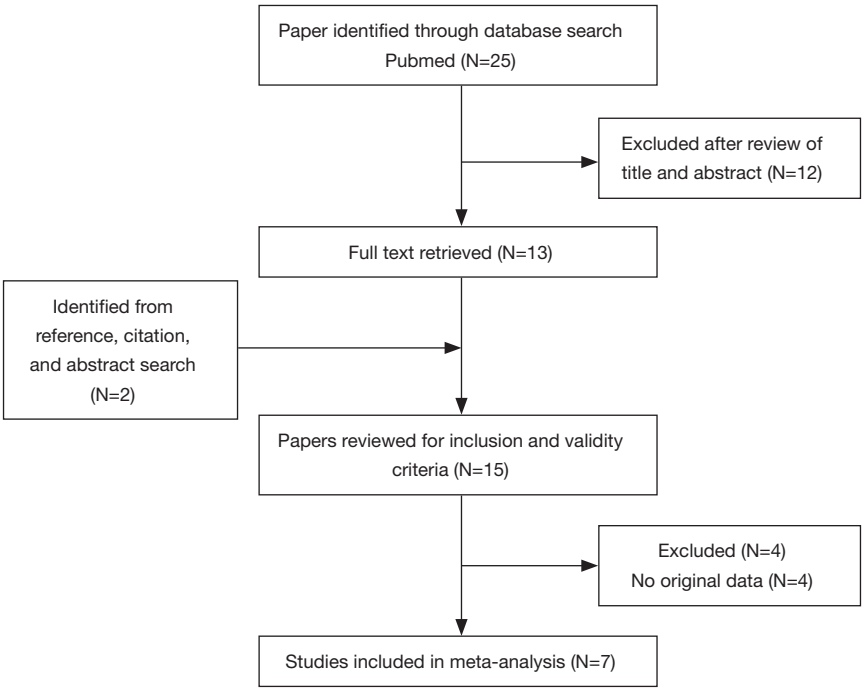

Figure 1 The literature search process. Twenty-five studies were identified in the primary literature search, and seven studies were finally included in the analysis according to the inclusion criteria.

(P=0.308, *Figure 3*).

Discussion

The systematic review and meta-analysis reported here showed that high serum LDH level is significantly associated with shorter PFS and OS times in mCRC patients treated with bevacizumab-based first-line chemotherapy, indicating that this parameter may be useful as a prognostic biomarker for this patient cohort. This result differs in some aspects from a similar meta-analysis of mCRC patients by Li *et al.*, which found that serum LDH level had prognostic value for OS but not PFS (6). However, the meta-analysis inclusion criteria differed between the two studies. First, we included only mCRC patients who were treated with bevacizumab as first-line chemotherapy, whereas Li *et al.* did not specify treatment with bevacizumab. Second, the method of LDH detection in the seven included studies here were to measure the LDH concentration in plasma, whereas two of the eligible studies in the analysis by Li *et al.* used immunohistochemical techniques, suggesting that the detection methods may have contributed to the discrepancy between studies. Therefore, we can conclude only that serum LDH may be a prognostic factor for PFS specifically in mCRC patients who were treated with bevacizumab.

The relationship between LDH and the outcome of anti-angiogenic treatment has been analyzed in several clinical trials. Two randomized phase III trials examined the efficacy of vatalanib (PTK/ZK), an oral angiogenesis inhibitor, in combination with FOLFOX (leucovorin, fluorouracil, oxaliplatin) for first-line (CONFIRM-1) and second-line (CONFIRM-2) therapy in mCRC patients (16,17). Although both studies failed to reach their primary end points, subgroup analysis showed that vatalanib improved the median PFS in patients with high serum LDH levels (16,17), supporting the possibility that LDH may be a predictive biomarker for anti-angiogenic therapy. In another study, Bar *et al.* retrospectively evaluated serum LDH levels obtained in the HORIZON I study, which was a randomized phase II head-to-head comparison of bevacizumab and cediranib, an oral VEGF receptor inhibitor, in mCRC patients. That analysis identified a significant correlation between high serum LDH and shorter PFS. Thus, the results of our meta-analysis are consistent with the conclusions of three previous studies identifying a correlation between serum LDH level and outcome for mCRC patients treated with bevacizumab.

Our study has several limitations. First, the number

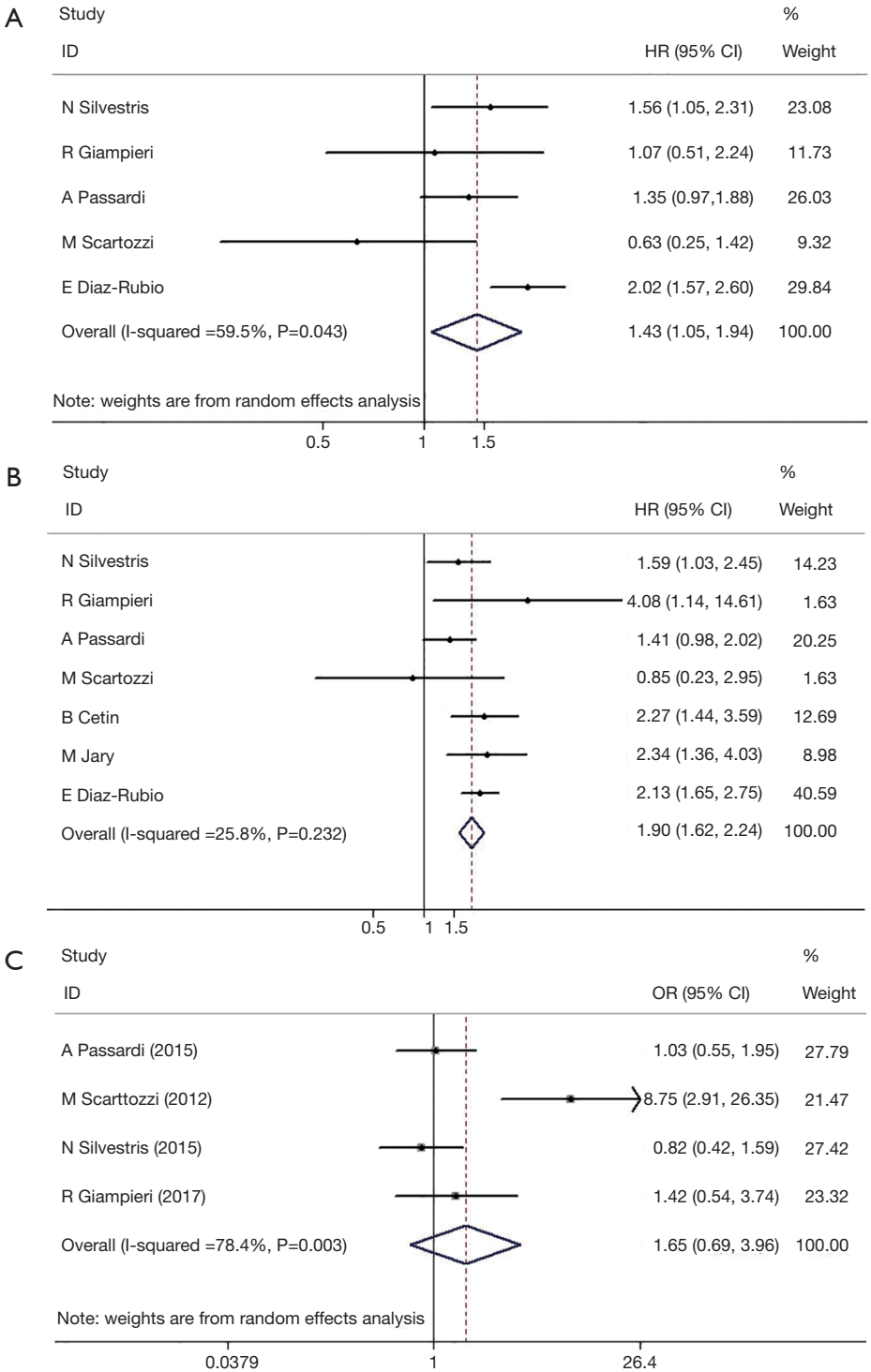

Figure 2 Meta-analysis of the association between lactate dehydrogenase serum level and (A) progression-free survival, (B) overall survival and (C) objective response rate.

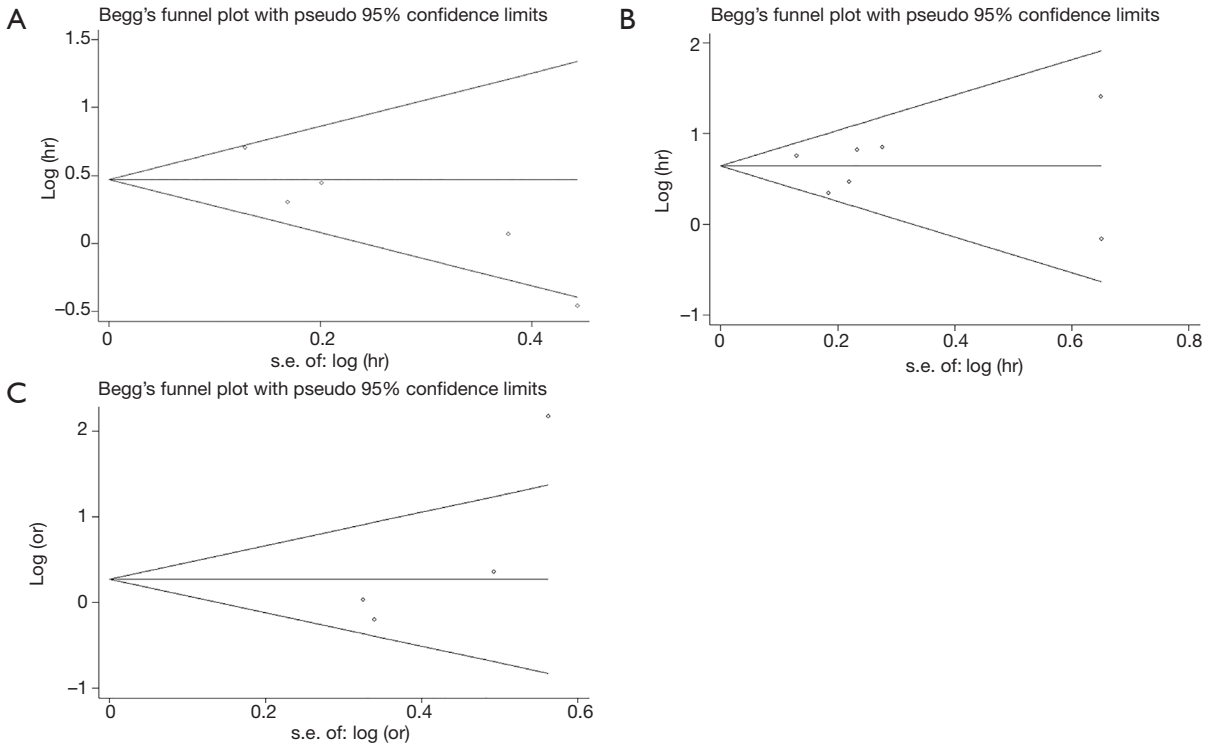

Figure 3 Test of publication bias of the analysis of lactate dehydrogenase serum level and (A) progression-free survival, (B) overall survival and (C) objective response rate.

of eligible studies was small, and most of them were retrospective, which indicates a lower level in the hierarchy of evidence-based medicine. Second, our meta-analysis was based only on studies meeting our inclusion criteria, whereas many others studies failed to meet these criteria. Third, we could not obtain updated data on individual patients, which would further enhance the accuracy and reduce the uncertainty of our estimates.

Conclusions

Our meta-analysis provides evidence that high serum LDH level is significantly associated with shorter PFS and OS time in mCRC patients treated with bevacizumab-based first-line chemotherapy. Serum LDH may thus be useful as a prognostic factor for patients receiving bevacizumab as first-line chemotherapy and as a predictive factor for those receiving bevacizumab-based therapy at other times.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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