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Review

Krüppel-like factor 4 expression in solid tumor prognosis: A meta-analysis

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ABSTRACT

Background: Accumulating studies have demonstrated that Krüppel-like factor 4 (KLF4) can act as a tumor suppressor or oncogene in the carcinogenesis of diverse cancers. The prognostic value of KLF4 in various human solid cancers remains controversial. Thus, the present meta-analysis was conducted to evaluate the prognostic value of KLF4 in solid tumors.

Methods: Eligible literature was retrieved by searching the PubMed, Embase, and Cochrane Library. Combined hazard ratios (HRs) for overall survival (OS) and disease-free survival (DFS) were assessed using fixed-effects and random-effects models. Meta-regression and subgroup analyses were performed to identify the source of heterogeneity. In addition, publication bias was assessed using Begg's funnel plot and Egger's regression asymmetry test.

Results: The 22 eligible studies finally enrolled a total of 2988 patients to assess the prognostic value of KLF4 in solid tumors. Low KLF4 expression was clearly related to worse OS (HR = 1.71, 95% confidence interval [CI] = 1.30–2.24, $P < 0.001$) and DFS (HR = 1.74, 95% CI = 1.34–2.26, $P < 0.001$), indicating that low KLF4 expression could be an independent prognostic factor for poor survival in solid cancers.

Conclusion: KLF4 might be a potential marker to predict prognosis in solid cancer patients.

1. Introduction

Due to the high rate of incidence and mortality, cancer is a worldwide public health challenge and causes more deaths than cardiovascular disease does in some countries [1]. Although targeted therapies and comprehensive treatments in some cancers have made rapid progress, the outcomes of the vast majority of patients with cancer remain poor. Thus, early detection and precise diagnosis may facilitate the selection of proper therapeutic treatments, which could improve the prognosis of patients with malignancies.

Krüppel-like factor 4 (KLF4), a member of the zinc finger transcription factors family that possesses a highly conserved C-terminal region composed of triple zinc fingers with DNA-binding activity [2, 3], participates in various biological processes, including cell proliferation, differentiation, and migration [4]. Recently, KLF4 has gained attention for its role in inducing pluripotent stem cells, as well as its diverse functions in physiology and pathophysiology. Several studies found that KLF4 could function as a tumor suppressor in multiple types of cancers such as gastrointestinal cancer [5], lung cancer [6], cervical cancer (CC) [7], breast cancer (BC) [8], liver cancer [9], and pancreatic ductal adenocarcinoma (PDAC) [10]. However, emerging evidence supported that KLF4 could act as an oncogene in specific cancer types [11–13]. KLF4 promotes the proliferation and migration of osteosarcoma cells through upregulating the expression of alpha-crystallin B chain (CRYAB) [13]. Additionally, KLF4 is overexpressed in BC and knockdown of KLF4 suppresses the migration and invasion of tumor cells [11].

A reliable and clinically relevant prognostic biomarker may indicate the progression of the underlying disease and help clinicians to select a more suitable treatment strategy. Recently, KLF4 has been reported to be closely associated with the prognosis of cancer patients. Most studies have shown that the worsening prognosis of cancer patients comes with decreasing expression of KLF4 in tumor tissues. There are numerous studies demonstrating that patients with KLF4 positive expression

Abbreviations: TNBC, triple-negative breast cancer; BC, breast cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; LAC, lung adenocarcinoma; NB, neuroblastoma; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; OC, ovarian cancer; CCRCC, clear cell renal cell carcinoma; CC, cervical cancer; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence intervals; RR, relative risk; UICC, Union for International Cancer Control; NR, not report; SC, survival curve; IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; ELISAs, enzyme-linked immunosorbent assays; TGF-β1, transforming growth factor-beta 1; CSCs, cancer stem cells; ESCs, embryonic stem cells

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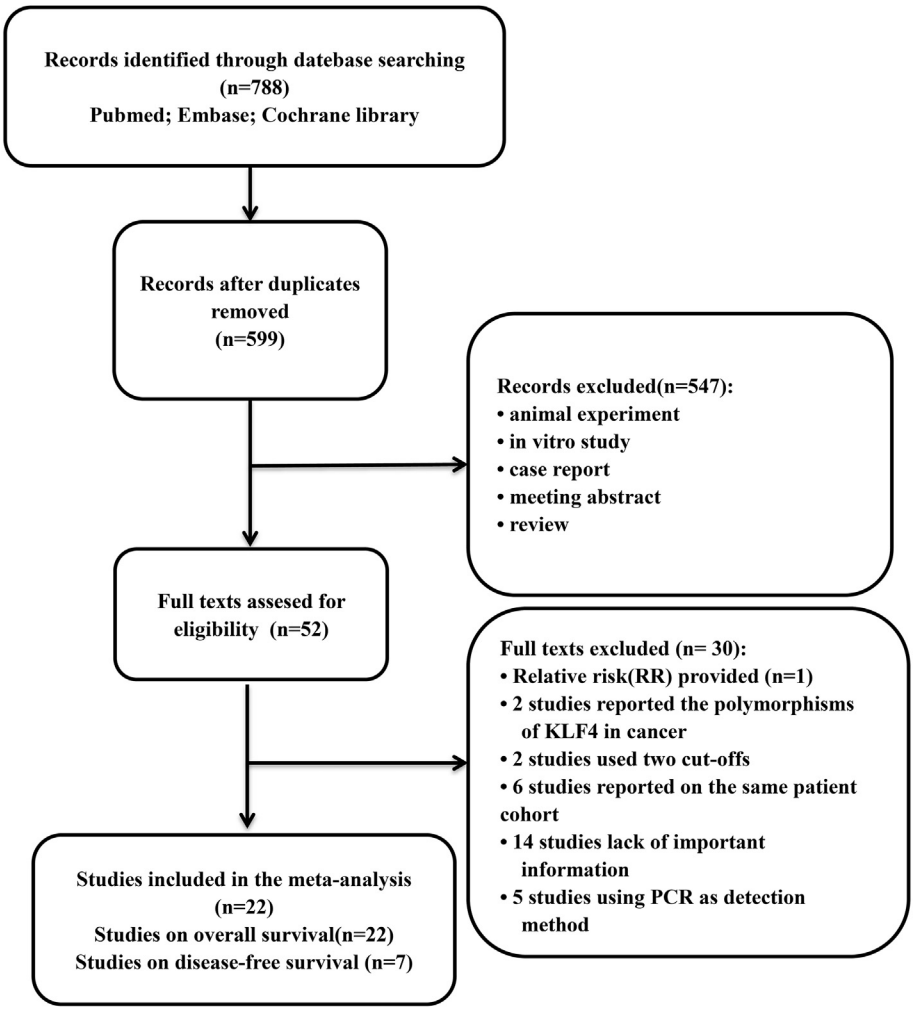

Fig. 1. Flow diagram of the studies identified in the meta-analysis.

experience a better overall survival (OS) in colorectal cancer (CRC) [14, 15], gastric cancer (GC) [16], renal cell cancer (RCC) [17], oral squamous cell cancer (OSCC) [18], and triple-negative breast cancer (TNBC) [19]. However, several emerging studies have suggested that a high KLF4 level was closely associated with poor survival. Lee et al. [20] reported that CRC patients with higher KLF4 level were more likely to develop recurrence and had poorer OS. Yin et al. [21] found that KLF4 positive expression levels were not only closely related to aggressive tumor behaviors including vascular invasion and poor differentiation, but also associated with worse OS and recurrence-free survival (RFS). These results suggested that the observed associations may be discordant because of different detection methods, cut-off values, sampling protocols, and/or other possible factors. Therefore, the effects of KLF4 on the clinical outcome of patients in various human solid cancers remain controversial. In the present study, we conducted a meta-analysis to evaluate the prognostic role of KLF4 in patients with solid tumors.

2. Materials and methods

The meta-analysis was performed according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology group (MOOSE) [22] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) [23].

2.1. Search strategy

We searched the online databases (PubMed, Embase, and Cochrane library) to retrieve relevant literature up to December 31, 2017. The search strategy applied was as follows: ("KLF4" OR "Kruppel-like factor 4" OR "gut-enriched Kruppel-like factor" OR "GKLF") AND ("cancer" OR "carcinoma" OR "tumor" OR "neoplasm") AND ("prognosis" OR "prognostic" OR "outcome" OR "survival"). To ensure the quality of the meta-analysis, the search and identification were independently performed by two authors (Miaomei Yu and Bo Hao) according to the standardized approach.

2.2. Study selection criteria

Studies that were included in the systematic review adhered to the following criteria: (i) the malignant disease was confirmed by histopathology; (ii) the expression of KLF4 was detected by immunohistochemistry, western blots, or enzyme-linked immunosorbent assays (ELISAs), but not PCR, due to the fact that expression of mRNA was unable to reflect the expression of protein; (iii) studies evaluating the association between KLF4 and the clinical outcome, including OS and disease-free survival (DFS); (iv) studies providing the hazard ratio (HR) with 95% confidence interval (CI) directly, or by indirect information such as Kaplan-Meier curves used to estimate survival data; and (v) when two or more studies reported on the same patient population, only the most recent report or the largest sample size was included to avoid overlapping between cohorts.