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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Prognostic role of glycolysis for cancer outcome: evidence from 86 studies

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Abstract

Objective The abnormal expression of the key enzymes in glycolytic pathways, including glucose transporter-1, glucose transporter-3, hexokinase-II, lactate dehydrogenase 5, pyruvate kinase M2, glucose-6-phosphate dehydrogenase, transketolase-like protein 1 and pyruvate dehydrogenase kinase-1 was reported to be associated with poor prognosis of various cancers. However, the association remains controversial. The objective of this study was to investigate the prognostic significance of glycolysis-related proteins.

Materials and methods We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, using Pubmed and Ovid as search engines and Google Scholar from inception to April 2017. Eighty-six studies with 12,002 patients were included in the study.

Results Our pooled results identified that glycolysis-related proteins in cancers were associated with shorter overall survival of colorectal cancer (HR 2.33, 95% CI 1.38–3.93, $P=0.002$), gastric cancer (HR 1.55, 95% CI 1.31–1.82, $P<0.001$), cancer of gallbladder or bile duct (HR 2.16, 95% CI 1.70–2.75, $P<0.001$), oral cancer (HR 2.07, 95% CI 1.32–3.25, $P<0.001$), esophageal cancer (HR 1.66, 95% CI 1.25–2.21, $P=0.01$), hepatocellular carcinoma (HR 2.04, 95% CI 1.64–2.54, $P<0.001$), pancreatic cancer (HR 1.72, 95% CI 1.39–2.13, $P<0.001$), breast cancer(HR 1.67, 95% CI 1.34–2.08, $P<0.001$), and nasopharyngeal carcinoma (HR 3.59, 95% CI 1.75–7.36, $P<0.001$). No association was found for lung cancer, ovarian cancer or melanoma. The key glycolytic transcriptional regulators (HIF-1α, p53) were analyzed in parallel to the glycolysis-related proteins, and the pooled results identified that high-level expression of HIF-1α was significantly associated with shorter overall survival (HR 0.57, 95% CI 0.42–0.79, $P<0.001$) Furthermore, glycolysis-related proteins linked with poor differentiated tumors (OR 1.81, 95% CI 1.46–2.25, $P<0.001$), positive lymph node metastasis (OR 2.73, 95% CI 2.16–3.46, $P<0.001$), positive vascular invasion (OR 2.05, 95% CI 1.37–3.07, $P<0.001$), large tumor size (OR 2.06, 95% CI 1.80–2.37, $P<0.001$), advanced tumor stage (OR 1.58, 95% CI 1.19–2.09, $P<0.001$), and deeper invasion (OR 2.37, 95% CI 1.93–2.91, $P<0.001$).

Conclusion Glycolytic transcriptional regulators and glycolysis-related proteins in cancers were significantly associated with poor prognosis, suggesting glycolytic status may be potentially valuable prognostic biomarkers for various cancers.

Keywords Prognostic markers · Survival · Cancer · Glycolysis · Systematic review · Meta-analysis

Min Yu, Shengying Chen, Weifeng Hong and Yujun Gu contributed equally to this work.

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Introduction

Re-programming of metabolic pathways is a hallmark of physiological changes in cancer cells (Furuta et al. 2010). Glycolysis and oxidative phosphorylation are the two important metabolic pathways associated with energy provision. Glycolysis, one of the most ancient metabolic processes, is a relatively low-energy-providing pathway compared with oxidative phosphorylation. Increased need for glycolysis, known as the Warburg effect, and glucose uptake for energy production have been identified in various cancers (Warburg 1956a, b; Warburg et al. 1927). Emerging data have demonstrated that cancer-specific aerobic glycolysis, which is characterized by increased glucose uptake, lactate export and extracellular acidification, has contributed to cancer initiation, progression, chemotherapy resistance and recurrence. Although oxidative catabolism is more efficient in ATP production, glycolysis was identified increased along with up-regulation of glucose transporters when the Krebs cycle is blocked in the presence of oxygen. Due to the highly activated level in various tumor tissues, the glycolysis status is considered to have potential prognostic value to predict patients' outcome. Over the last decades, in vitro, vivo and clinical studies have implicated the key enzymes in glycolytic pathways, including glucose transporter-1 (GLUT1), glucose transporter-3 (GLUT3), hexokinase-II (HKII), lactate dehydrogenase 5 (LDH5), pyruvate kinase M2 (PYK-M2), glucose-6-phosphate dehydrogenase (GLC6PDH), transketolase-like protein 1 (TKTL1), and pyruvate dehydrogenase kinase-1 (PDK-1) as potential candidate biomarkers for survival of lung cancer, gastric cancer, pancreatic cancer, hepatocellular carcinoma, breast cancer and so on. However, inconsistent results were reached. To the best of our knowledge, meta-analysis data on the correlation of glycolysis-related proteins with the prognosis and clinicopathological features of patients with various tumors are already unavailable. Thus, the present study was carried out to investigate the glycolysis-related proteins in various cancers and its relationship with prognosis and clinicopathological features of various cancer patients.

Among the key enzymes in glycolysis, most widely used markers including GLUT1, GLUT3, HKII, LDH5, PYK-M2, GLC6PDH, TKTL1, and PDK-1 were selected as glycolysis-related protein marker.

GLUT1 fuels glycolysis through increased uptake of glucose across membrane, which is the first rate-limiting step in glycolysis. Increased expression of GLUT1 contributes to enhanced glycolysis (Kitamura et al. 2011). GLUT3 largely mediates basal glucose transport in cancer cells, facilitating the maintenance of glycolytic energy metabolism in cases of limited supply of the substrate in moderately to poorly perfused regions (Kallinowski et al. 1989). HKII is located in both mitochondria and cytosol, and catalyzes the first step of glycolytic pathway where glucose is converted to glucose-6-phosphate HKII (Pauwels et al. 2000). PYK-M2, an alternatively spliced variant of pyruvate kinase, catalyzes the conversion of phosphoenolpyruvate to pyruvate, which is an essential step in process of glycolysis (Christofk et al. 2008a, b). LDH5 was identified as a key checkpoint of glycolysis because it drives the conversion of pyruvate to lactate. LDH5 executes the final step of aerobic glycolysis and has been considered to be engaged in the tumor initiation and progression (Giatromanolaki et al. 2006; Kolev et al. 2008). Both glucose-6-phosphate dehydrogenase (GLC6PDH) and transketolase-like-1 (TKTL1) participated in an important branch of glycolysis, pentose phosphate pathway (Bentz et al. 2013; Ho et al. 2007; Kuo et al. 2000). PDK-1, one of the four known isozymes of pyruvate dehydrogenase kinases, acts to inactivate the function of pyruvate dehydrogenase and thus inhibits pyruvate recruitment into the tricarboxylic acid cycle (Zhao et al. 2011). Therefore, glycolysis-related proteins above have been shown to be engaged in process of glycolysis.

The key glycolytic transcriptional regulators such as HIF-1alfa and p53 play important roles in glycolysis. p53, a well-studied tumor suppressor, plays a critical role in controlling numerous cellular processes, including apoptosis, cell cycle arrest, and genomic stability. p53 is also known to reduce the glycolysis rate by increasing the activity of a fructose-2,6-bisphosphatase which is involved in the regulatory pathways of apoptosis (Bensaad et al. 2006; Bensinger and Christofk 2012). Therefore, a reduced expression of protein p53 in cancer cells was linked to the Warburg effect in regulating cell apoptosis.

Recent studies have revealed a number of new functions of p53 in the regulation of glucose and energy metabolic pathways, including glucose transport (Symmans et al. 2007), glycolysis (Bensaad et al. 2006), tricarboxylic acid cycle (Contractor and Harris 2012), mitochondrial respiratory chain/oxidative phosphorylation (Matoba et al. 2006), and PPP (McArdle et al. 1992; Gottlieb 2011).

Hypoxia-inducible factor-1 alpha (HIF-1α) is known as a key regulatory factor of tissue adaptation under hypoxia. It is highly expressed in most tumors and metastases, and is inseparable from the glycolytic pathway of tumor cells (Lum et al. 2007). Related glycolytic genes regulated by HIF-1α include the GLUT-1, lactate dehydrogenase A (LDHA), phosphofructokinase 2 (PFK2), aldolase A, enolase 1, phosphoglycerate kinase 1 and glyceraldehyde-3-phosphate dehydrogenase coding genes. HIF-1 induced the expression of the above genes to enhance glycolysis to meet the needs of energy metabolism when the process of oxidative phosphorylation was inhibited by the condition

of hypoxia (Yu et al. 2008; Elson et al. 2000; Ashrafian 2006).

Methods

Search strategy

An extensive search of articles and abstracts was conducted in all major electronic databases from inception to April 2017, using the following MeSH terms and text words: "glycolysis", "Warburg effect", "Immunohistochemistry", "tumor(s)", "cancer(s)", "carcinoma(s)", "malignant", "neoplasm(s)", "survival", "prognosis or prognostic or outcome", "survival", and "HR". Two reviewers (Yu and Hong) independently conducted a search of EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane database of Systematic Reviews, using PubMed and Ovid as search engines as well as Google Scholar. Finally, we scrutinized the reference lists of all relevant articles to identify studies that may not have been identified by the strategy outlined above.

Inclusion and exclusion criteria

Articles which passed the primary screening were further scrutinized for the presence of all the following items: (1) cohort studies or case–control studies, which were concerned about the relationship between prognostic role of glycolysis and cancer; (2) cancer diagnosis must be clearly proved; (3) the hazard ratio and 95% confident intervals were best characterized by sufficient information; (4) ruling out such studies which were concerning animals or cell lines and even case-series, letters, editorials, comments, reviews, and abstracts. Those studies that lead us to no detailed information to estimate the hazard ratio and 95% confident intervals were also excluded, even though contacts with relevant authors had been made.

Data collection process and data synthesis

Eligible studies and data were extracted using a standardized data collection form to increase the uniformity of data extraction. The reviewers had a discussion to resolve the inconsistencies between their data until consistency was reached. The relation between glycolysis and overall survival or disease-free survival of cancer patients in each study was extracted as the hazard ratio and 95% confident interval. Studies that only provided overall survival curves and/or disease-free survival curve were processed for extracting the hazard ratio and 95% confident intervals based on the method previously described.

Assessment of study quality

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies which were performed. A star system has been developed for the assessment. It is feasible for us to set a study awarded 0–3, 4–6, or 7–9 stars as a low-, moderate-, or high-quality study dividedly as previously described. The selected studies were evaluated independently by two investigators (Yu and Hong) in a blinded fashion. Besides, any inconsistency would be solved by discussion with the third investigators (Gu).

Statistical analysis

We performed meta-analysis using Review Manager (version 5.3 for Windows) and Stata (version 12 for Windows). HR and 95% CI were used to compare the different impacts of driver status on survival of patients, whereas OR with 95% CI was applied to assess the association between the level of glycolystic enzymes and clinicopathological features. HRs and corresponding 95% CIs of low expression versus high expression were adopted in some studies, then we calculated reciprocal to get high-expression versus low-expression data (Tierney et al. 2007). In cases of no direct HR and corresponding 95% CI found in some studies, we using the methods developed by Parmar et al. (1998), Williamson et al. (2002) and Tierney et al. (2007) to estimate these values based on available data, such as survival curves. In our meta-analysis, heterogeneity was assessed by the chi-square test and P value. The I^2 value was used to assess heterogeneity, and if $I^2 = 0–50\%$, a fixed-effect model is used, meaning there is no significant heterogeneity. Otherwise, the random-effect model was applied. The illustration of the HRs and 95% CIs of each included study was shown by forest plots and the results were pooled. Funnel plots were used to assess evidence for publication bias. Sensitivity analysis was conducted by extraction of each single study to investigate the stability of the results and the resource of heterogeneity. All P values were two sided, being statistically significant when the P value is less than 0.05.

Results

Literature search

Detailed search steps are depicted in Fig. 1. Eighty-six studies were selected for further analysis in the present meta-analysis. All clinicopathological features of the 86 eligible studies are presented in Tables 1 and 2. These observational studies consisted of 12,002 cancer patients. Glycolysis-related protein markers included glucose transporter-1 (GLUT1), hexokinase-II (HKII), lactate dehydrogenase 5

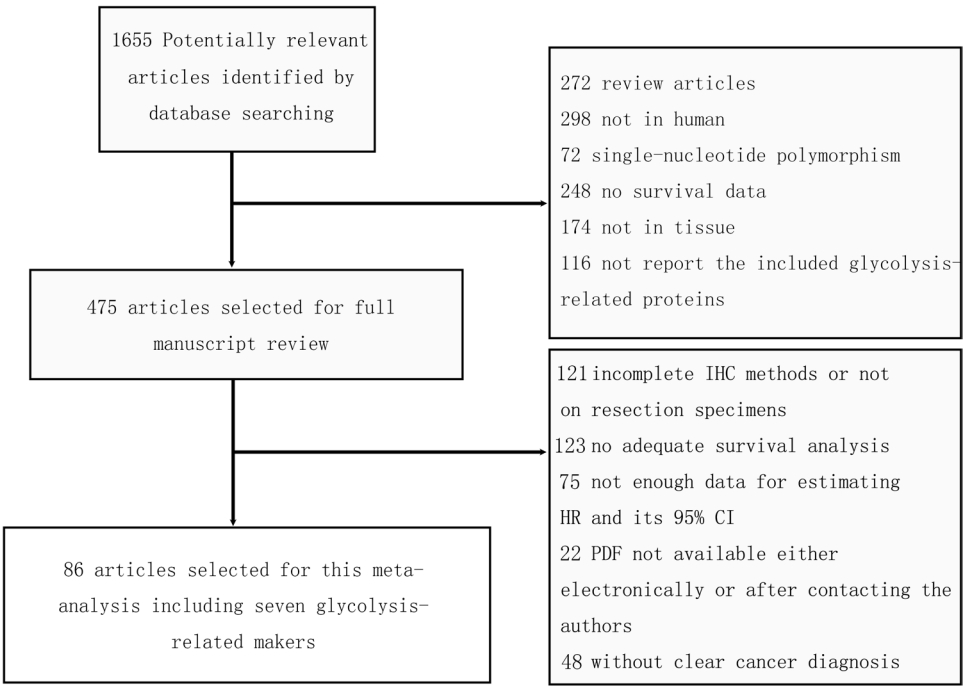


Fig. 1 Flow diagram of study selection

(LDH5), pyruvate kinase M2 (PYK-M2), glucose-6-phosphate dehydrogenase (GLC6PDH), and transketolase-like protein 1 (TKTL1), pyruvate dehydrogenase kinase-1 (PDK-1). Of these selected studies, 31 articles reported relation between GLUT1 and prognosis (Furudoi et al. 2001; Kawamura et al. 2001; Kang et al. 2002; Kim et al. 2002; Mineta et al. 2002; Hoskin et al. 2003; Sebastiani 2004; Lyshchik et al. 2007; Mori et al. 2007; Fenske et al. 2009; Sung et al. 2010; Andersen et al. 2011; Kitamura et al. 2011; Jang et al. 2012), four reported GLUT3 (Baer et al. 2002; Zhou et al. 2008; Ayala et al. 2010; Schlosser et al. 2017), 11 reported HKII, 11 reported LDH5 (Koukourakis et al. 2003, 2006, 2009; Giatromanolaki et al. 2006; Kolev et al. 2008; Danner et al. 2010; Kayser et al. 2010; Zhuang et al. 2010; Grimm et al. 2013a, b; Lu et al. 2013; Kim et al. 2014), 19 reported PYK-M2 (Benesch et al. 2010; Lim et al. 2012; Hjerpe et al. 2013; Karachaliou et al. 2013; Zhan et al. 2013; Zhang et al. 2013; Li et al. 2014a, b; Yuan et al. 2014; Chen et al. 2015; Gao et al. 2015; Hu et al. 2015), three reported GLC6PDH (Wang et al. 2012, 2015a, b, Pu et al. 2015), four reported TKTL1 (Foldi et al. 2007; Fritz et al. 2012; Grimm et al. 2013a, b; Song et al. 2015), and three reported PDK-1 (Kim et al. 2013; Yang et al. 2014; Dai et al. 2016). Among the eligible studies, 74 articles reported overall survival (Baer et al. 2002; Koukourakis et al. 2003, 2006; Giatromanolaki et al. 2006; Foldi et al. 2007; Rho et al. 2007; Kolev et al. 2008; Zhou et al. 2008; Ayala et al. 2010; Schlosser et al. 2017; Furudoi et al. 2001; Kawamura et al. 2001; Kang et al. 2002; Kim et al. 2002; Hoskin et al. 2003; Lyshchik et al. 2007; Mori et al. 2007). Twenty articles evaluated disease-free survival as end point (Kolev et al. 2008; Zhuang et al. 2010; Grimm et al. 2013a, b; Kim et al. 2013; Kang et al. 2002; Sebastiani 2004; Fenske et al. 2009; Andersen et al. 2011; Kitamura et al. 2011; Jang et al. 2012; Kwon et al. 2013; Maki et al. 2013), seven evaluated PFS (Karachaliou et al. 2013; Suh et al. 2014; Huang et al. 2015; Pu et al. 2015; Dong et al. 2016; Zhang et al. 2016a, b; Iwasaki et al. 2015), three evaluated RFS (Lim et al. 2012; Mineta et al. 2002; Sawayama et al. 2014), two evaluated CSS (Sato-Tadano et al. 2013; Sawayama et al. 2014), and one evaluated TTR (Liu et al. 2015).

Correlation of glycolysis-related proteins with survival

A meta-analysis was performed on 70 studies assessing the association of glycolysis-related proteins with overall survival. The pooled HR was 1.69 (95% CI 1.54–1.86; $P = 0.000$), with significant heterogeneity ($I^2 = 51\%$, $P = 0.000$) (Fig. 2a). To investigate the source of heterogeneity, subgroup analysis by types of glycolysis-related proteins, sample size, categories of diseases, study location and study quality was performed. As depicted in Table 3, subgroup analysis suggested that several increased expression of glycolysis-related proteins were correlated with poor survival, including GLUT1 (HR 1.77, 95% CI 1.50–2.08, $P = 0.000$), HKII (HR 2.17, 95% CI 1.72–2.74, $P = 0.000$), PYK-M2 (HR 1.71, 95% CI 1.46–1.99, $P = 0.008$), GLC6PDH (HR 2.01, 95% CI 1.37–2.95, $P = 0.000$), and PDK-1 (HR 1.61, 95% CI

Table 1 Characteristics of included studies in this analysis

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
GLUT1											
Furudoi et al. (2001)	Japan	R	Colorectal carcinoma	39/72	1983–1994	MA	OS	3.90 (1.08–4.03)	Poor	8	Lymph node metastasis, lymphatic invasion, venous invasion, Ki-67
Kawamura et al. (2001)	Japan	R	Gastric carcinoma	77/105	1987–1989	MA	OS	1.410 (1.039–1.914)	Poor	8	Gender, age, histologic type, depth of invasion, lymph factor, T factor, N factor, stage
Mineta et al. (2002)	Japan	R	Hypopharyngeal carcinoma	46/53	NR	UA	RFS	0.486 (0.263–0.897)	Poor	7	NR
Kang et al. (2002)	Korea	R	Breast cancer	47/53	1996–1997	UA	OS DFS	1.10 (0.25–4.81) 2.67 (0.59–12.12)	Poor Poor	6	NR
Kim et al. (2002)	Korea	R	Gallbladder cancer	37/34	1981–1999	MA	OS	2.080 (0.922–4.694)	NS	8	GLUT1, cerbB-2, stage, diagnosis, sex, age
Hoskin et al. (2003)	UK	R	Bladder cancer	29/45	NR	MA	OS	3.14 (1.23–10.09)	Poor	7	Age, T stage and grade
Sebastiani (2004)	Italy	R	Endometrial carcinoma	58/29	1992–1996	MA	DFS	1.01 (0.80–1.27)	NS	7	Age, grade, histological type, stage
Mori et al. (2007)	Japan	R	Primary salivary gland tumor	39/13	1990–2005	MA	OS	4.379 (1.232–15.559)	Poor	9	Age, gender, tumor size, lymph node metastasis
Lyshchik et al. (2007)	Japan	R	Pancreatic cancer	33/41	NR	UA	OS	1.30 (0.89–1.92)	Indeterminate	7	NR
Fenske et al. (2009)	Germany	R	Adrenocortical carcinoma	35/101	NR	MA	OS DFS	1.45 (0.81–2.96) 1.36 (0.59–3.19)	NS NS	8	NR
Fenske et al. (2009)	Germany	R	Adrenocortical carcinoma	16/101	NR	MA	OS DFS	6.34 (3.10–12.90) 6.01 (2.16–16.94)	Poor Poor	8	NR
Kitamura et al. (2011)	Japan	R	Hepatocellular carcinoma	23/40	2003–2005	UA	DFS	3.32 (0.92–12.30)	Poor	6	NR
Sung et al. (2010)	Korea	R	Ampulla of vater cancer	38/29	1983–2007	UA	OS	0.66 (0.28–1.53)	NS	6	NR
Sung et al. (2010)	Korea	R	Pancreatic cancer	27/25	1983–2007	UA	OS	1.50 (0.93–2.43)	NS	6	NR
Sung et al. (2010)	Korea	R	Extrahepatic bile duct cancer	38/83	1983–2007	UA	OS	1.74 (0.98–2.64)	NS	6	NR
Sung et al. (2010)	Korea	R	Gallbladder cancer	53/62	1983–2007	UA	OS	2.33 (1.47–3.69)	Poor	6	NR

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Andersen et al. (2011)	Norway	R	Non-small cell lung cancer	62/46	1990–2004	UA	DFS	2.0 (1.1–3.4)	Poor	6	T-status, N-status, vascular infiltration
Jang et al. (2012)	Korea	R	Breast cancer	156/265	2000–2009	MA	OS	2.845 (1.204–6.724)	Poor	8	AJCC stage, lymphatic invasion, perinodal tumor extension
							DFS	2.057 (1.124–3.764)	Poor		
Sasaki et al. (2012)	Japan	R	Lung carcinoma	138/145	2001–2008	UA	OS	1.64 (0.92–2.92)	Poor	7	NR
Maki et al. (2013)	Japan	R	Lung cancer	28/77	2004–2006	MA	DFS	6.02 (1.25–48.22)	Poor	8	Age, gender, Smoking status, tumor size, Ki-67, EGFR, KRAS
Kim et al. (2013)	Korea	R	Cervical cancer	37/125	1996–2010	MA	OS	1.85 (0.322–10.61)	NS	8	NR
							DFS	0.96 (0.44–2.11)			
Kwon et al. (2013)	Korea	R	Phyllodes tumors	5/202	2000–2010	MA	OS	0.5 (0.00–5.0)	NS	7	Stromal cellularity, stromal atypia, stromal mitosis, stromal overgrowth, tumor margin, stromal GLUT1, stromal CAIX, stromal MCT4
							DFS	0.8 (0.1–5.1)	NS		
Cho et al. (2013)	Korea	R	Ovarian cancer	26/24	2008–2010	UA	OS	1.36 (0.24–7.57)	NS	7	NR
Ramani et al. (2013)	UK	R	Neuroblastic tumors	44/52	1994–2011	UA	OS	2.44 (0.99–6)	Poor	7	NR
Sawayama et al. (2014)	Japan	R	Esophageal squamous cell carcinoma	41/104	2000–2008	UA	RFS	2.021 (1.100–3.712)	Poor	7	NR
							CSS	2.223 (1.121–4.411)	Poor		
Yu et al. (2015)	China	R	Pancreatic cancer	62/44	2000–2012	MA	OS	1.781 (1.024–2.843)	Poor	8	Tumor differentiation, nerve infiltration, glut-1 in tumor, got1 in tumor, LC3 in tumor, BNIP3 in tumor, metabolism subtypes, number of metabolism types
Osugi et al. (2015)	Japan	R	Lung cancer	75/59	1998–2000	MA	OS	0.660 (0.243–1.787)	NS	7	Tumor size, lymph node, p-stage, GLUT1, ACLY, GLUT1 + ACLY

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Goos et al. (2016)	Dutch	R	Colorectal cancer	107/107	1990–2010	UA	OS	1.515 (1–2.326)	NS	8	NR
Starska et al. (2015)	Poland	R	Laryngeal cancer	89/17	2003–2011	UA	OS	1.22 (0.47–3.16)	NS	7	NR
Iwasaki et al. (2015)	Japan	R	Cervical cancer	40/15	NR	MA	PFS	2.375 (0.109–52.632)	NS	8	FIGO stage, histology, lymph–vascular space involvement, microvessel density, HIF1α, CA-IX, VEGF
Berlth et al. (2015)	Germany	R	Gastric adenocarcinoma	62/62	1996–2007	MA	OS	1.716 (1.352–2.206)	Poor	8	UICC, Lauren classification, R category
Boström et al. (2016)	Canada	R	Bladder cancer	78/21	NR	MA	DFS	2.9 (0.7–12.6)	NS	7	T-category
Boström et al. (2016)	Finland	R	Bladder cancer	142/38	NR	MA	DFS	3.2 (1.3–7.5)	Poor	7	T-category, N-category, lymphovascular invasion
Lu et al. (2016)	China	R	Pancreatic cancer	39/14	2000–2011	MA	OS	3.401 (1.761–6.536)	Poor	8	Gender, age, tumor location, tumor size, clinical stage, differentiation, lymph node metastasis, vascular invasion
Yan et al. (2016)	China	R	Melanoma	53/46	1994–2008	MA	OS	0.97 (0.29–3.21)	NS	8	Tumor thickness, mitoses rate, ulceration, ProEx C
Swartz et al. (2016)	Netherland	R	Oropharyngeal squamous cell carcinomas	65/188	1997–2011	UA	OS	1.502 (1.049–2.151)	Poor	7	NR
GLUT3											
Ayala et al. (2010)	Brazil	R	Oral squamous cell carcinoma	30/112	2003–2011	MA	OS	1.933 (1.119–3.339)	Poor	8	Vascular embolization
Baer et al. (2002)	USA	R	Laryngeal carcinoma	30/18	NR	UA	OS	1.72 (0.55–5.35)	NS	6	NR
Schlosser et al. (2017)	Germany	R	Gastric cancer	93/48	2006–2011	MA	OS	1.852 (1.044–3.284)	Poor	8	Lauren, Stage, R, Sex, Age, Chemotherapy
Zhou et al. (2008)	China	R	Head and neck carcinoma	21/17	2003–2005	UA	OS	2.01 (0.78–5.21)	NS	6	NR
HKII											
Rho et al. (2007)	Korea	R	Gastric carcinoma	43/214	1995–1995	UA	OS	1.468 (0.942–2.288)	Indeterminate	8	Pathological stage

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Qiu et al. (2011)	China	R	Gastric carcinoma	40/148	1999–2001	MA	OS	3.475 (1.564–7.721)	Poor	5	Tumor size, HIF1α, tumor stage
Gong et al. (2012)	China	R	Hepatocellular carcinoma	39/41	NR	UA	OS	2.049 (1.022–4.110)	Poor	8	NR
Kwee et al. (2012)	America	R	Hepatocellular carcinoma	74/85	1986–2009	MA	OS	1.62 (1.00–2.60)	Poor	8	Tumor size, stage
Sato-Tadano et al. (2013)	Japan	R	Breast cancer	52/66	2004–2008	MA	DFS CSS	2.65 (1.10–6.90) 0.53 (0.79–25.4)	Poor Poor	8	Ki-67, T factor, lymph node metastasis, histologic grade, microvessel density, ER status, VEGF, MDR-1, menopausal status, HER2 status, HIF1α
Suh et al. (2014)	Korea	R	Ovarian cancer	55/55	2003–2009	MA	OS PFS	1.81 (0.66–4.93) 2.63 (1.41–4.92)	Poor Poor	8	Advanced stage, high-grade tumor, non-optimal debulking
Ogawa et al. (2015)	Japan	R	Pancreatic cancer	21/15	2007–2012	MA	OS	2.57 (0.89–8.39)	Indeterminate	7	pT stage, nodal metastasis, PYK-M2
Huang et al. (2015)	China	R	Cervical carcinoma	77/55	2005–2012	MA	PFS	2.940 (1.609–5.790)	Poor	7	Age, FIGO stage, histopathological grade, tumor diameter
Katagiri et al. (2016)	Japan	R	Colorectal cancer	100/95	2000–2008	MA	OS DFS	2.7 (1.4–5.6) 2.5 (1.3–4.9)	Poor Poor	8	Lymph node metastasis, tumor location, depth of invasion, liver metastasis
Zhang et al. (2016a, b)	China	R	Nasopharyngeal carcinoma	92/48	2004–2008	MA	PFS OS	4.366 (1.461–13.049) 4.845 (1.633–14.375)	Poor Poor	8	Gender, age, T stage, N stage, TNM stage
Zhang et al. (2016)	China	R	Hepatocelluar carcinoma	66/89	2000–2013	UA	OS	2.70 (1.76–4.15)	Poor	7	NR
LDH5											
Koukourakis et al. (2003)	UK	R	Non-small-cell lung cancer	53/59	NR	MA	OS	1.37 (0.73–2.57)	Poor	9	HIF1α/LDH-5, HIF2α/LDH-5, CA9, N factor, T factor, VEFG, histology
Giatromanolaki et al. (2006)	Greece	R	Endometrial carcinoma	31/37	NR	MA	OS	1.48 (0.10–10.89)	Poor	8	Grade, depth, vascular invasion, PgR, ER, HIF1α, HIF2α, VEFGR2, VEGF, sVD

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Koukourakis et al. (2003)	UK	R	Colorectal cancer	98/30	NR	MA	OS	1.53(0.17–13.47)	Poor	9	Tumor size, lymph node metastasis, TN, VI, HIF1α, VEGF, pKDR, sVD, aVD
Kolev et al. (2008)	Japan	R	Gastric carcinoma	94/58	1992–1999	MA	OS DFS	2.49 (1.22–5.13) 2.79 (1.22–6.41)	Poor Poor	8	HIF1α, COX-2, VEGF
Koukourakis et al. (2009)	UK	R	Head and neck cancer	65/25	NR	MA	OS	0.74 (0.24–2.31)	Poor	7	T factor, N factor, grade, HIF1α, HIF2α
Koukourakis et al. (2009)	UK	R	Head and neck cancer	24/15	NR	MA	OS	1.30 (0.25–6.82)	Poor	7	T factor, N factor, grade, HIF1α, HIF2α
Zhuang et al. (2010)	Australia	R	Melanoma	39/54	2000–2003	MA	OS DFS	3.170 (0.403–24.967) 3.201 (0.448–22.844)	Poor Poor	6	Age, gender, mitotic rate Breslow thickness, Clark level, ulceration, histopathological type, perineural invasion
Danner et al. (2010)	Germany	R	Non-small cell lung cancer	54/17, medium	2000–2006	UA	OS	1.04 (0.75– 1.35)	Poor	6	NR
Danner et al. (2010)	Germany	R	Non-small cell lung cancer	18/17, high	2000–2006	UA	OS	0.50 (0.20–1.27)	Poor	6	NR
Kayser et al. (2010)	Germany	R	Lung cancer	241/28	1989–2004	UA	OS	0.56 (0.35–0.88)	Indeterminate	5	NR
Lu et al. (2013)	China	R	Non-Hodgkin Lymphoma	94/172	2006–2012	MA	OS	1.061 (0.759–1.483)	Indeterminate	5	Age, gender, histological type, Extra-nodal sites involvement, WHO performance status
Grimm et al. (2013a, b)	Germany	R	Oral carcinoma	49/142	NR	UA	DFS	14.379 (7.0815–29.1995)	Poor	8	Lymph node metastasis
Kim et al. (2014)	Korea	R	Gastric carcinoma	219/159	2004–2004	UA	OS DFS	1.49 (0.89–2.47) 1.65 (1.07–2.53)	Indeterminate Poor	6	NR
PYK-M2											
Benesch et al. (2010)	Germany	R	Breast cancer	112/48	1985–1995	UA	OS	1.35 (0.77–2.37)	Indeterminate	7	NR
Lim et al. (2012)	Korea	R	Gastric carcinoma	144/224	1999–2007	UA	OS RFS	0.92 (0.65–1.30) 0.93 (0.66–1.32)	Indeterminate Indeterminate	8	NR
Hjerpe et al. (2013)	Sweden	P	Ovarian cancer	28/26	2003–2008	MA	OS	1.1 (0.5–2.2)	Indeterminate	9	GAPDH, ATP5B, BEC-index
Karachaliou et al. (2013)	India	R	Small cell lung cancer	26/38	NR	MA	OS PFS	1.39 (0.96–1.83) 1.32 (0.93–1.82)	Indeterminate Indeterminate	5	ERCC1, TOPOI, TOPOIIA, TOPOIIB

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Zhan et al. (2013)	China	R	Esophageal cancer	83/42	2006–2006	UA	OS	1.08 (0.45– 0.64)	Indeterminate	8	NR
Zhang et al. (2013)	China	R	Esophageal cancer	84/42	2006–2006	UA	OS	1.50 (0.69–3.27)	Indeterminate	8	NR
Zhang et al. (2013a, b)	China	R	Esophageal carcinoma	62/24	NR	MA	OS	2.358 (0.156–4.812)	Poor	9	Age, gender, tumor size, differentiation, AJCC stage, lymph node metastasis
Li et al. (2014a, b)	China	R	Gallbladder cancer	26/20	1995–2009	MA	OS	2.680 (1.090–6.591)	Poor	8	Differentiation, tumor size, TNM stage, lymph metastasis, invasion, ACVR 1C metastasis
Li et al. (2014a, b)	China	R	Gallbladder cancer	45/35	1995–2009	MA	OS	2.210 (1.299–3.759)	Poor	8	Differentiation, tumor size, TNM stage, lymph metastasis, invasion, ACVR 1C
Chen et al. (2015)	China	R	Hepatocellular carcinoma	77/159	2007–2007	UA	OS	3.125 (2.00–5.00)	Poor	7	NR
Liu et al. (2015)	China	R	Hepatocellular carcinoma	89/278	2009–2010	MA	OS TTR	1.901 (1.321–2.737) 1.451 (1.067–1.973)	Poor Poor	7	HBsAg, AFP, γ-GT, tumor size, microvascular invasion, tumor differentiation, TNM stage
Li et al. (2014a, b)	China	R	Esophageal squamous cell carcinoma	59/82	2007–2009	MA	OS	1.214 (0.728–2.026)	Indeterminate	8	Tumor size, T stage, N stage, differentiation, TNM stage, HK1
Kim et al. (2014)	China	R	Tongue squamous cell carcinoma	42/21	2001–2010	MA	OS	6.015 (1.512–23.932)	Poor	8	Age, gender, Histopathological grade, Tumor size, combined chemotherapy, local vessel/nerve invasion, cervical nodal metastasis, clinical stage, LDH5 expression
Hu et al. (2015)	China	R	Hepatocellular carcinoma	331/307	2000–2010	MA	OS DFS	1.675 (1.389–2.019) 1.573 (1.214–2.038)	Poor	7	NR
Yu et al. (2015a, b)	China	R	Hilar cholangiocarcinoma	47/41	2004–2008	UA	OS DFS	2.43 (1.20–4.93) 2.83 (1.54–5.19)	Poor Poor	7	NR

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Zhao et al. (2015)	China	R	Cervical cancer	90/42	2005–2012	MA	DFS	2.888 (1.347–6.194)	Poor	8	Age, FIGO stage, histopathological grade, tumor diameter, combined chemotherapy
Dong et al. (2016)	China	R	Breast cancer	135/160	2003–2009	UA	OS	1.841 (1.398–2.424)	Poor	7	NR
							PFS	2.648 (1.865–3.266)			
Wang et al. (2015a, b)	China	R	Oral squamous cell carcinoma	63/48	2005–2011	MA	OS	3.118 (1.445–5.082)	Poor	7	Gender, Age, primary site. tumor size, pathological grade, local recurrence, cervical nodal metastasis, distant metastasis, clinical stage
Gao et al. (2015)	China	R	Gastric cancer	47/77	2002–2005	MA	OS	1.232 (0.674–2.254)	Indeterminate	8	Tumor size, T stage, N stage, differentiation, TNM stage, HK1
Lockney et al. (2015)	America	R	Pancreatic ductal adenocarcinoma	61/54	2000–2009	MA	OS	1.754 (1.099–2.778)	Poor	7	Age, surgical margin status, perineural invasion, peripancreatic extension
Mohammad et al. (2016)	Germany	R	Pancreatic cancer	46/26	2005–2010	UA	OS	1.72 (1.01–2.92)	Poor	7	NR
Glc6PDH											
Wang et al. (2012)	China	R	Gastric carcinoma	116/51	2010–2010	MA	OS	1.759 (1.127–2.747)	Poor	7	Tumor size, HT, depth of invasion, lymph metastasis, distant metastasis, TNM stage
Wang et al. (2015a, b)	China	R	Esophageal carcinoma	95/33	NR	MA	OS	3.006 (1.342–6.732)	Poor	6	Gender, age, Lymph metastasis, clinical stage, histologic grade
Pu et al. (2015)	China	R	Breast cancer	8/12	2005–2014	MA	OS	2.695 (0.271–26.815)	NS Poor	7	Tumor stage, tumor size, PYK-M2
							PFS	13.488 (1.472–123.554)			
TKTL1											
Foldi et al. (2007)	Germany	R	Breast cancer	56/68	1990–1999	UA	OS	0.99 (0.49–2.02)	NS	7	NR

Table 1 (continued)

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
Grimm et al. (2013a, b)	Germany	R	Oral cancer	68/93	NR	MA	OS	3.5315 (1.7333–7.1956)	Poor	9	Lymph node metastasis, UICC stage, Apo10, L factor
Fritz et al. (2012)	Germany	R	Lung cancer	42/107	NR	UA	OS	1.11 (0.85–1.46)	Indeterminate	8	NR
Song et al. (2015)	China	R	Gastric cancer	56/45	2004–2005	MA	OS	2.043 (1.195–3.493)	Poor	8	Depth of invasion, tumor differentiation level, TNM stage, number of lymph node metastasis, p63 expression
PDK-1											
Kim et al. (2013)	Korea	R	Gastric carcinoma	67/554	2003–2006	MA	OS	1.337 (0.914–1.956)	Indeterminate, Indeterminate	8	Age, CEA, stage, NUAK2, pAMPK, MAPK3/1
							DFS	1.391 (0.950–2.037)			
Yang et al. (2014)	China	R	Esophageal squamous cell carcinoma	65/55	2002–2009	UA	OS	1.78 (1.04–3.05)	Poor	7	NR
Dai et al. (2016)	China	R	Nasopharyngeal carcinoma	23/59	2004–2009	MA	OS	2.849 (1.094–7.407)	Poor	8	T classification, clinical stage, SDHB expression

CC case–control, *NCC* nested case–control, *RFS* relapse-free survival, *PFS* progression-free survival, *OS* overall survival, *DFS* disease-free survival, *CSS* cancer-specific survival, *TTR* time to recurrence, *R* retrospective, *UA* univariate analysis, *MA* multivariate analysis

Table 2 Characteristics of staining in included studies

Reference	Antibody source	Dilution	Counting method	Definition of positive
GLUT1				
Furudoi et al. (2001)	Polyclonal, DAKO	NR	Percentage of positive cells	> 30% of tumor cells
Kawamura et al. (2001)	Polyclonal, Chemicon	1:4000	Percentage of positive cells	> 30% of positive cells
Mineta et al. (2002)	Polyclonal, Chemicon	1:1000	Percentage of positive cells	> 70% of positive cells
Kang et al. (2002)	Polyclonal, DAKO	1:200	Percentage of positive cells	Absence of positive cells
Kim et al. (2002)	Polyclonal, DAKO	1:200	Percentage of positive cells	Absence of positive cells
Hoskin et al. (2003)	Polyclonal, DAKO	1:200	Percentage of positive cells	> 10% cells with positive
Sebastiani (2004)	Monoclonal, NA	NR	Combination of staining intensity score and percentage of positive cells	> 6
Mori et al. (2007)	Polyclonal, DAKO	1:50	Percentage of positive cells	> 15% of positive cells
Lyshchik et al. (2007)	Polyclonal, DAKO	1:200	Percentage of positive cells	> 40% of positive cells
Fenske et al. (2009)	Polyclonal, DAKO	1:100	Percentage of positive cells	> 10% of positive cells
Kitamura et al. (2011)	Polyclonal, DAKO	1:200	Percentage of positive cells	> 0% of positive cells
Sung et al. (2010)	Polyclonal, DAKO	1:200	Percentage of positive cells	> 5% of positive cells
Andersen et al. (2011)	Monoclonal, abcam	1:500	Combination of staining intensity score and percentage of positive cells	> 1
Jang et al. (2012)	Monoclonal, abcam	1:250	Percentage of positive cells	> 10% of positive cells
Sasaki et al. (2012)	Monoclonal, Thermo Scientific	NA	NA	NA
Maki et al. (2013)	Monoclonal, abcam	1:200	Percentage of positive cells	> 10% of positive cells
Kim et al. (2013)	Monoclonal, NeoMarkers	1:3000	Combination of staining intensity score and percentage of positive cells	> 1
Kwon et al. (2013)	Monoclonal, abcam	1:200	Percentage of positive cells	> 10% of positive cells
Cho et al. (2013)	Monoclonal, R&D Systems	NA	Combination of staining intensity score and percentage of positive cells	> 3.85
Ramani et al. (2013)	Polyclonal, Merck-Millipore	NA	NA	NA
Sawayama et al. (2014)	Polyclonal, abcam	1:7500	Percentage of positive cells	> 50% of positive cells
Yu et al. (2015a, b)	NA	NA	Combination of staining intensity score and percentage of positive cells	≥ 2
Osugi et al. (2015)	Polyclonal, DAKO	1:500	Percentage of positive cells	> 50% of positive cells
Goos et al. (2016)	Polyclonal, abcam	1:600	Combination of staining intensity score and percentage of positive cells	NA
Starska et al. (2015)	Polyclonal, abcam	1:1000	Combination of staining intensity score and percentage of positive cells	≥ 5
Iwasaki et al. (2015)	NR, abcam	1:200	Percentage of positive cells	> 50%
Berlth et al. (2015)	Polyclonal, Thermo Fisher Scientific	1:200	Percentage of positive cells	> 10%
Boström et al. (2016)	Polyclonal, DAKO	1:2000	NR	> 0
Lu et al. (2016)	Monoclonal, abcam	1:300	Combination of staining intensity score and percentage of positive cells	> 1
Yan et al. (2016)	NR, abcam	1:200	Combination of staining intensity score and percentage of positive cells	> 0
Swartz et al. (2016)	NR, DAKO	1:100	Percentage of positive cells	> 66% of positive cells
GLUT3				
Ayala et al. (2010)	Polyclonal, Lab Vision Corporation	NR	Percentage of positive cells	> 10%

Table 2 (continued)

Reference	Antibody source	Dilution	Counting method	Definition of positive
Baer et al. (2002)	Polyclonal, Chemicon International	1:1000	NR	NR
Schlosser et al. (2017)	NR, DAKO	1:100	Percentage of positive cells	> 10%
Zhou et al. (2008)	Polyclonal, DAKO	1:50	NR	NR
HKII				
Rho et al. (2007)	NR, Santa Cruz	1:100	Percentage of positive cells	> 10%
Qiu et al. (2011)	Polyclonal, Santa Cruz	1:200	NR	NR
Gong et al. (2012)	Polyclonal, Santa Cruz	NR	Percentage of positive cells	> 10%
Kwee et al. (2012)	Monoclonal, cell signaling technology	1:100	Intensity of staining	> 0
Sato-Tadano et al. (2013)	Monoclonal, cell signaling technology	1:100	Combination of staining intensity score and percentage of positive cells	> 4
Suh et al. (2014)	Polyclonal, Santa Cruz	1:100	combination of the percentage of positively stained cells and staining intensity	> 10% of cells with a staining intensity of at least grade 1
Ogawa et al. (2015)	Monoclonal, cell signaling technology	1:400	Combination of staining intensity score and percentage of positive cells	≥ 5
Huang et al. (2015)	NR, cell signaling technology	1:600	Percentage of positive cells	≥ 25%
Katagiri et al. (2016)	Monoclonal, cell signaling technology	NR	Percentage of positive cells	> 10%
Zhang et al. (2016a, b)	Polyclonal, Thermo Scientific	1:150	Combination of staining intensity score and percentage of positive cells	> 3
Zhang et al. (2016)	Monoclonal, cell signaling technology	1:50	Combination of staining intensity score and percentage of positive cells	> 3
LDH5				
Koukourakis et al. (2003)	Polyclonal, Abcam	1:200	Percentage of positive cells	> 10% of cells with nuclear LDH-5
Giatromanolaki et al. (2006)	Polyclonal, Abcam	NR	Percentage of positive cells	① Strong cytoplasmic in more than 50% of tumor cells ② High nuclear in more than 10% of tumor cells
Koukourakis et al. (2006)	Polyclonal, Abcam	1:400	Percentage of positive cells	> 30% of positive cells
Kolev et al. (2008)	Polyclonal, Abcam	1:500	Percentage of positive cells	① Strong cytoplasmic in more than 50% of tumor cells ② High nuclear in more than 10% of tumor cells
Koukourakis et al. (2009)	Polyclonal, Abcam	1:400	Percentage of positive cells	① Strong cytoplasmic in more than 50% of tumor cells ② High nuclear in more than 10% of tumor cells
Zhuang et al. (2010)	Polyclonal, Abcam	1:400	Combination of staining intensity score and percentage of positive cells divided by 10	> 15
Danner et al. (2010)	Polyclonal, Abcam	NR	Semi-quantitative scaling with five levels (< 10–25%, 25–50%, 50–75%, > 75%, respectively)	> 25%
Kayser et al. (2010)	Polyclonal, Abcam	NR	Percentage of positive cells	> 50%
Lu et al. (2013)	NR	NR	NR	> 250
Grimm et al. (2013a, b)	Polyclonal, Abcam	1:200	Percentage of positive cells	> 10% of positive cells

Table 2 (continued)

Reference	Antibody source	Dilution	Counting method	Definition of positive
Kim et al. (2014)	Polyclonal, Abcam	NR	Percentage of positive cells	① Strong cytoplasmic in more than 50% of tumor cells ② High nuclear in more than 10% of tumor cells
PYK-M2				
Benesch et al. (2010)	Monoclonal, ScheBo Biotech AG	1:250	Combination of staining intensity score and percentage of positive cells	> 4
Lim et al. (2012)	NR, cell signaling technology	1:500	Percentage of positive cells	> 25%
Hjerpe et al. (2013)	NR	NR	Staining intensity score and percentage of positive cells	≥ 20% tumor cells staining 3+
Karachaliou et al. (2013)	NR	NR	NR	NR
Zhan et al. (2013)	NR	1:3000	Combination of staining intensity score and percentage of positive cells	> 1
Zhang et al. (2013)	Polyclonal, Abgent	1:30	Combination of staining intensity score and percentage of positive cells	> 4
Li et al. (2014a, b)	NR	1:100	Percentage of positive cells	> 25%
Chen et al. (2015)	NR	1:800	Staining intensity score	> 0
Liu et al. (2015)	NR	NR	Staining intensity score and percentage of positive cells	Moderate staining in one-third to two-thirds of the cells or strong staining in more than two-thirds of the cells
Li et al. (2014a, b)	NR, EPITOMICS	1:100	Combination of staining intensity score and percentage of positive cells	≥ 0.75
Kim et al. (2014)	NR, cell Signaling	1:200	Combination of staining intensity score and percentage of positive cells	> 4
Hu et al. (2015)	NR, cell signaling technology	1:1000	Combination of staining intensity score and percentage of positive cells	> 3
Yu et al. (2015a, b)	NR	1:100	Combination of staining intensity score and percentage of positive cells	≥ 75
Zhao et al. (2015)	NR, Abcam	1:600	Percentage of positive cells	> 25%
Dong et al. (2016)	Monoclonal, OriGene	1:10,000	Combination of staining intensity score and percentage of positive cells	> 1
Wang et al. (2015a, b)	NR, cell signaling	1:250	Combination of staining intensity score and percentage of positive cells	≥ 4
Gao et al. (2015)	NR, EPITOMICS	1:100	Intensity of staining	> 0
Lockney et al. (2015)	Polyclonal, cell signaling technology	1:800	Combination of staining intensity score and percentage of positive cells	> 0
Mohammad et al. (2016)	Monoclona, lScheBo Biotech	1:100	Combination of staining intensity score and percentage of positive cells	> 3
Glc6PDH				
Wang et al. (2012)	Polyclonal, Abcam	1:200	Combination of staining intensity score and percentage of positive cells	> 4

Table 2 (continued)

Reference	Antibody source	Dilution	Counting method	Definition of positive
Wang et al. (2015a, b)	NR, Santa Cruz	1:100	Combination of staining intensity score and percentage of positive cells Staining cells × staining intensity	≥ 1
Pu et al. (2015)	NR	NR	Combination of staining intensity score and percentage of positive cells	≥ 10% cells moderate or strong straining
TKTL1				
Foldi et al. (2007)	Monoclonal, NR	NR	Percentage of positive cells	> 20%
Grimm et al. (2013a, b)	Monoclonal, TAVARTIS GmbH	1:100	Combination of staining intensity score and percentage of positive cells	> 0
Fritz et al. (2012)	Monoclonal, TAVARTIS GmbH	1:30	Combination of staining intensity score and percentage of positive cells	> 150
Song et al. (2015)	Polyclonal, Abcam	NR	Combination of staining intensity score and percentage of positive cells	≥ 3
PDK-1				
Kim et al. (2013)	Polyclonal, Santa Cruz	1:100	Percentage of positive cells	> 10%
Yang et al. (2014)	Polyclonal, cell signaling technology	1:100	Combination of staining intensity score and percentage of positive cells	> 3.69
Dai et al. (2016)	Monoclonal, Abcam	1:500	Combination of staining intensity score and percentage of positive cells	≥ 4

1.14–2.25, $P = 0.006$), whereas there was not significant correlation between LDH5, TKTL1, GLUT3 and survival. But heterogeneity was significant in GLUT1 ($I^2 = 43\%$, $P = 0.010$) and PYK-M2 ($I^2 = 49\%$, $P = 0.007$). Results also demonstrated that higher expression of glycolysis-related proteins was correlated with worse OS in Asian (HR 1.75, 95% CI 1.53–2.01, $P = 0.000$) and Europe (HR 1.41, 95% CI 1.15–1.73, $P = 0.001$), while heterogeneity was significant in Asian ($I^2 = 76\%$, $P = 0.000$) and Europe ($I^2 = 63\%$, $P = 0.000$). No significant result was found between higher expression of glycolysis-related proteins and worse OS in America (HR 1.46, 95% CI 0.98–2.18, $P = 0.07$), since there are only four studies, it needs more data to substantiate this conclusion. Importantly, we found that significant link between glycolysis-related proteins and overall survival existed in cancers of digestive system without any significant heterogeneity across studies except colorectal cancer, such as gastric cancer (HR 1.55, 95% CI 1.31–1.82, $P < 0.001$; $I^2 = 39\%$, $P = 0.08$), cancer of gallbladder or bile duct (HR 2.16, 95% CI 1.70–2.75, $P = 0.000$; $I^2 = 0\%$, $P = 0.95$), esophageal cancer (HR 1.66 95% CI = 1.25–2.21, $P = 0.001$; $I^2 = 9\%$, $P = 0.360$), hepatocellular carcinoma (HR 2.04, 95% CI 1.64–2.54, $P = 0.000$; $I^2 = 46\%$, $P = 0.100$) pancreatic cancer (HR 1.72, 95% CI 1.39–2.13, $P = 0.000$; $I^2 = 14\%$, $P = 0.320$), and colorectal cancer (HR 2.33, 95% CI = 1.38–3.93, $P = 0.000$; $I^2 = 52\%$, $P = 0.010$). Significant link also existed in relation between overall survival and glycolysis-related proteins in oral cancer (HR 2.07, 95% CI 1.32–3.25, $P < 0.001$), but heterogeneity was significant ($I^2 = 84$, $P < 0.001$). Significant link was also found in breast cancer (HR 1.67, 95% CI 1.34–2.08, $P = 0.000$; $I^2 = 0\%$, $P = 0.430$) and nasopharyngeal carcinoma (HR 3.59, 95% CI 1.75–7.36, $P = 0.001$; $I^2 = 0\%$, $P = 0.470$). There was no significant association between prognosis and glycolysis-related proteins in lung cancer (HR 1.03, 95% CI = 0.80–1.32, $P = 0.810$; $I^2 = 57\%$, $P = 0.02$), ovarian cancer (HR 1.32, 95% CI = 0.75–2.31, $P = 0.34$; $I^2 = 0\%$, $P = 0.740$), and melanoma (HR 1.31, 95% CI = 0.46–3.70, $P = 0.61$; $I^2 = 0\%$, $P = 0.330$).

As disease-free survival (DFS) and progression-free survival (PFS) were reported in several articles, meta-analyses were also performed to evaluate the association of glycolysis-related proteins with DFS and PFS. Results showed that there was a significant association between glycolysis-related proteins and DFS with significant heterogeneity (HR 2.27, 95% CI = 1.72–2.99,

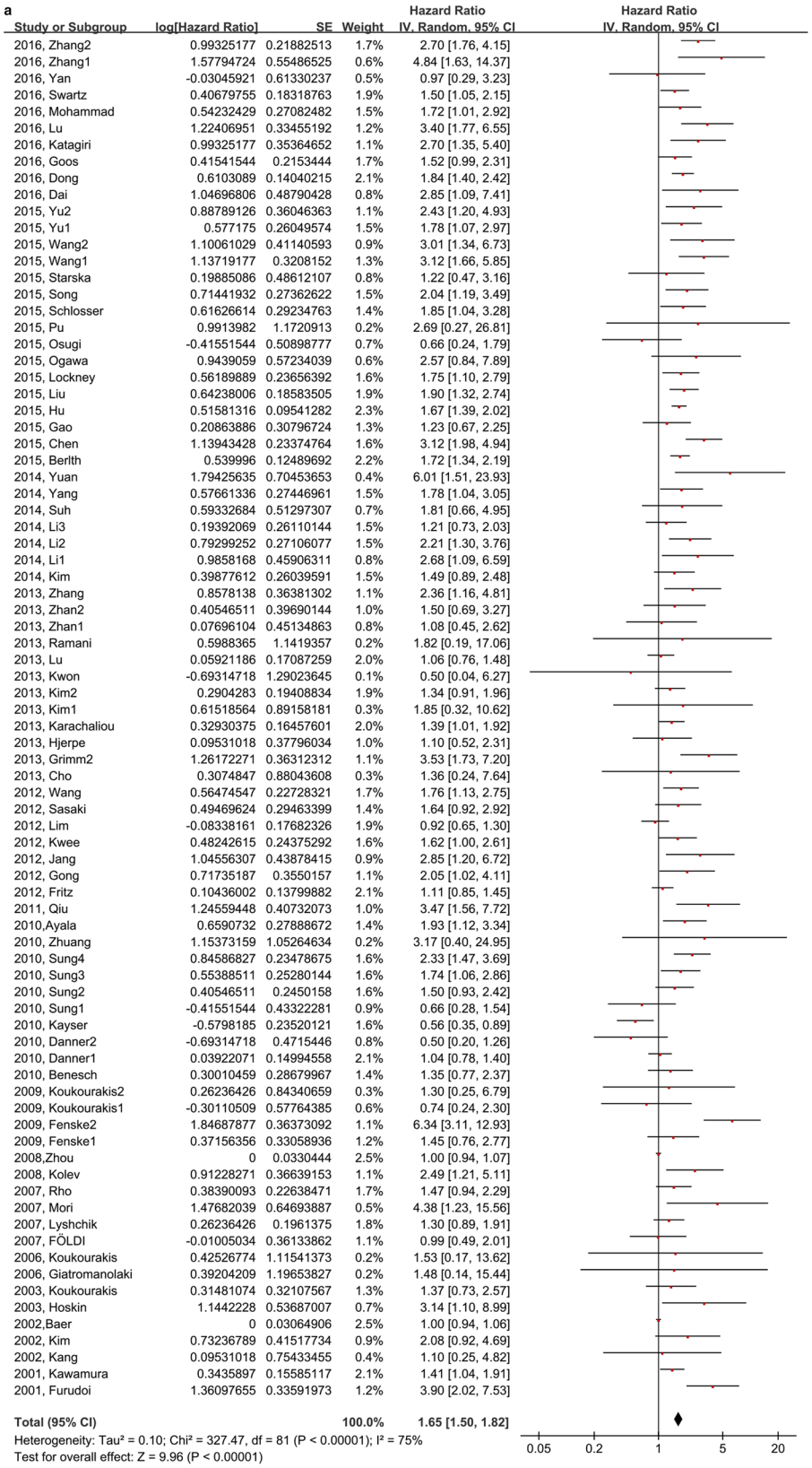
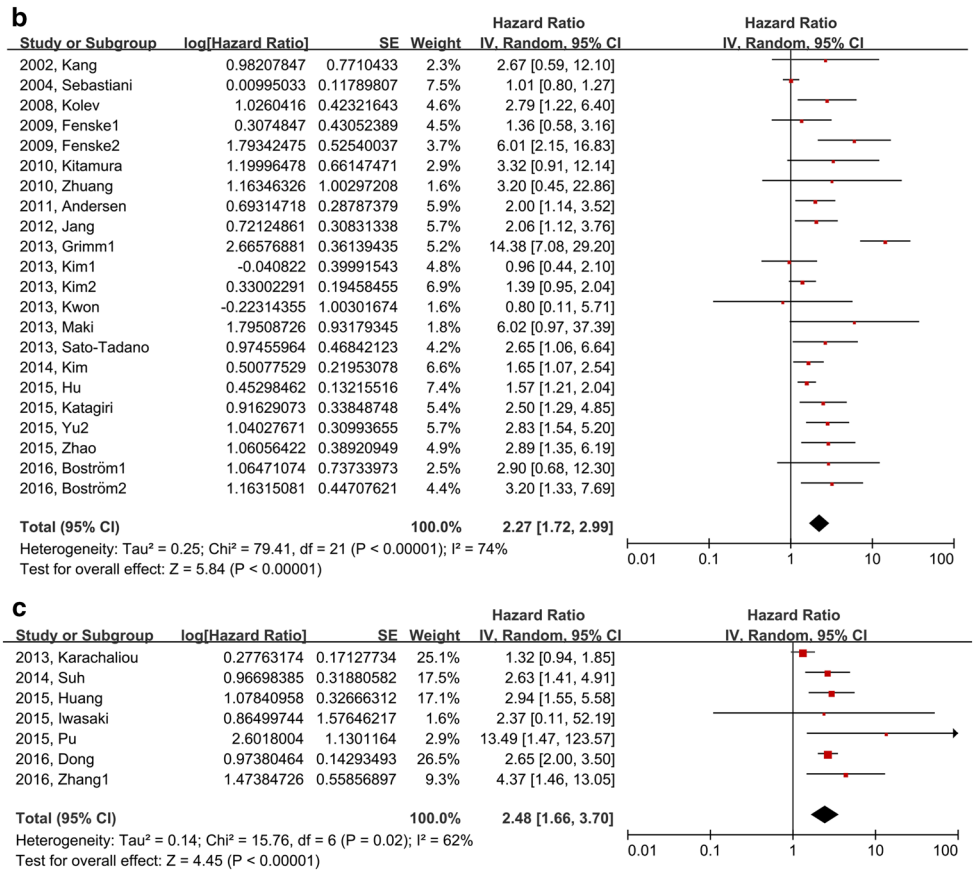


Fig. 2 Forest plot of hazard ratio (HR) for the association between glycolysis-related proteins and OS **a**, DFS (**b**) and PFS (**c**)

Fig. 2 (continued)



$P = 0.000$; $I^2 = 74\%$, $P = 0.000$) (Fig. 2b). A significant association also found between glycolysis-related proteins and PFS with significant heterogeneity (HR 2.48, 95% CI = 1.66–3.70, $P = 0.000$; $I^2 = 62\%$, $P = 0.020$) (Fig. 2c).

Correlation of the key glycolytic transcriptional regulators with survival

Some included studies have reported the key glycolytic transcriptional regulators such as HIF-1α (Kolev et al. 2008; Qiu et al. 2011; Andersen et al. 2011; Kim et al. 2002, 2013a, b; Kwon et al. 2013; Berlth et al. 2015; Starska et al. 2015; Bostrom et al. 2016; Goos et al. 2016; Swartz et al. 2016) and p53 (Dong et al. 2016; Kang et al. 2002; Sung et al. 2010). We analyze the association between prognosis and key glycolytic transcriptional regulators (HIF-1α, p53) in parallel to the glycolysis-related proteins. All characteristics of the studies for glycolytic transcriptional regulators are listed in Table 4. The pooled results identified that high-level expression of HIF-1α was significantly associated with shorter overall survival (HR 0.57, 95% CI 0.42–0.79, $P < 0.001$, $I^2 = 64\%$, $P = 0.01$) (Supplemental Fig. 1A), and shorter disease-free survival (HR 0.54, 95% CI 0.37–0.77, $P < 0.001$, $I^2 = 41\%$, $P = 0.14$) (Supplemental Fig. 1B), and mutation of p53 was significantly associated with shorter overall survival (HR 0.38, 95% CI 0.28–052, $P < 0.001$, $I^2 = 19\%$, $P = 0.27$) (Supplemental Fig. 2).

Correlation of the key glycolytic transcriptional regulators with glycolysis-related proteins

The correlation of the key glycolytic transcriptional regulators with glycolysis-related proteins is shown in Table 5. Significant correlation was found between Glc6PDH and p53 (Dong et al. 2016), while no significant correlation was observed between GLUT1 and p53 (Kang et al. 2002; Kim et al. 2002; Sung et al. 2010). For HIF-1α, it was found to have significant correlation with LDH5 (Kolev et al. 2008) and HK-II (Qiu et al. 2011), and some studies found that HIF-1α have significant correlation with GLUT1 (Kim et al. 2013a, b; Kwon et al. 2013; Berlth et al. 2015; Starska et al. 2015; Goos et al. 2016) while some studies did not support this conclusion (Andersen et al. 2011; Bostrom et al. 2016; Swartz et al. 2016).

Table 3 Stratified analysis for OS

Stratified analysis	Number of studies	Number of patients	Pooled HR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	*P* value
Antibodies						
GLUT1	23	3580	1.77 (1.50–2.08)	0.000	43	0.010
GLUT3	4	369	1.05 (0.94–1.18)	0.390	70	0.020
HKII	9	1320	2.17 (1.72–2.74)	0.000	15	0.310
LDH5	10	1701	1.08 (0.83–1.41)	0.560	43	0.050
PYK-M2	18	3359	1.71 (1.46–1.99)	0.000	49	0.007
TKTL1	4	535	1.62 (0.96–2.74)	0.070	75	0.007
Glc6PDH	3	315	2.01 (1.37–2.95)	0.000	0	0.510
PDK-1	3	823	1.61 (1.14–2.25)	0.006	16	0.300
Study location						
Asian	49	8652	1.75 (1.53–2.01)	0.000	76	0.000
Europe	20	2793	1.41 (1.15–1.73)	0.001	63	0.000
America	4	464	1.46 (0.98–2.18)	0.07	79	0.002
Sample size						
> 100	48	10,074	1.72 (1.54–1.92)	0.000	58	0.000
< 100	26	1928	1.34 (1.17–1.54)	0.000	60	0.000
Categories of diseases						
Colorectal cancer	4	648	2.33 (1.38–3.93)	0.002	52	0.100
Gastric cancer	12	2803	1.55 (1.31–1.82)	0.000	39	0.080
Lung cancer	7	1129	1.03 (0.80–1.32)	0.810	57	0.020
Cancer of gallbladder and bile duct	4	521	2.16 (1.70–2.75)	0.000	0.0	0.950
Oral cancer	7	924	2.07 (1.32–3.25)	0.002	84	0.000
Esophageal cancer	5	726	1.66 (1.25–2.21)	0.001	9.0	0.360
Hepatocellular carcinoma	6	1635	2.04 (1.64–2.54)	0.000	46	0.100
Breast cancer	7	1327	1.67 (1.34–2.08)	0.000	0.0	0.430
Pancreatic cancer	7	508	1.72 (1.39–2.13)	0.000	14	0.320
Ovarian cancer	3	214	1.32 (0.75–2.31)	0.340	0.0	0.740
Melanoma	2	192	1.31 (0.46–3.70)	0.610	0.0	0.330
Nasopharyngeal carcinoma	2	222	3.59 (1.75–7.36)	0.001	0.0	0.470
Quality of studies						
High quality	62	9883	1.77 (1.61–1.95)	0.000	40	0.000
Moderate quality	12	2119	1.19 (1.03–1.36)	0.020	72	0.000

Correlation of glycolysis-related proteins with clinicopathological features

The results showed that significant associations existed between glycolysis-related proteins and biologically aggressive phenotypes such as large tumor size (pooled OR 2.06, 95% CI 1.80–2.37) (Fig. 3a), poor tumor differentiation (pooled OR 1.81, 95% CI 1.46–2.25) (Fig. 3b), advanced tumor stage (pooled OR 1.58, 95% CI 1.19–2.09) (Fig. 3c), deeper invasion (pooled OR 2.37, 95% CI 1.93–2.91) (Fig. 3d), positive lymph node metastasis (pooled OR 2.73, 95% CI 2.16–3.46) (Fig. 3e), and positive vascular invasion (pooled OR 2.05, 95% CI 1.37–3.07) (Fig. 3f). Significant association did not exist between glycolysis-related proteins and male gender (pooled OR 1.11, 95% CI 0.99–1.25) (Fig. 3g), while no significant association was found between glycolysis-related proteins and age (pooled OR 0.99, 95% CI 0.83–1.18) (Fig. 3h).

Meta-regression and sensitivity analysis

Due to the high heterogeneity in the analysis of correlation of prognosis and glycolysis-related proteins, subgroup analysis (Tables 3, 6, 7) and meta-regression model were applied utilizing the variables as antibody subtypes, disease subtypes, geographic region, sample size and study quality to explore the potential source of heterogeneity found in these analyses. The results showed no variables contributing to the

Table 4 Characteristics of studies for glycolytic transcriptional regulators in this analysis

References	Country	Study design	Cancer types	Positive/negative, no.	Recruitment time	Analysis of variance	End point	Hazard ratios	Conclusion	Study quality	Factors included in multivariate analysis to identify independent factors influencing survival
HIF-1α											
Kolev et al. (2008)	Japan	R	Gastric carcinoma	95/57	1992–1999	MA	OS DFS	0.88 (0.48–1.62) 1.02 (0.5–2.07)	Poor NS	8	LDH-5, COX-2, VEGF
Qiu et al. (2011)	China	R	Gastric carcinoma	40/148	1999–2001	MA	OS	0.44 (0.29–0.68)	Poor	5	Tumor size, HKII, tumor stage
Andersen et al. (2011)	Norway	R	Squamous cell lung cancer	17/171	1990–2004	MA	DFS	0.3 (0.15–0.59)	Poor	6	T-status, N-status, vascular infiltration; differentiation
Kim et al. (2013)	Korea	R	Cervical cancer	60/91	1996–2010	UA	OS DFS	0.46 (0.14–0.91) 0.41 (0.18–1.03)	Poor NS	8	NR
Goos et al. (2016)	Dutch	R	Colorectal cancer	102/226	1990–2010	UA	OS	0.93 (0.67–1.29)	NS	8	NR
Starska et al. (2015)	Poland	R	Laryngeal cancer	76/30	2003–2011	UA	OS	0.29 (0.09–0.90)	Poor	7	NR
Swartz et al. (2016)	Netherland	R	Oropharyngeal squamous cell carcinomas	146/114	1997–2011	MA	OS	0.63 (0.44–0.89)	Poor	7	NR
Boström et al. (2016)	Canada	R	Bladder cancer	78/21	NR	UA	DFS	0.48 (0.16–1.43)	NS	7	NR
Boström et al. (2016)	Finland	R	Bladder cancer	142/38	NR	UA	DFS	0.77 (0.30–2.00)	NS	7	NR
Berlth et al. (2015)	Germany	R	Gastric adenocarcinoma	46/78	1996–2007	UA	OS	0.85 (0.55–1.31)	NS	8	NR
p53											
Kim et al. (2002)	Korea	R	Gallbladder cancer	48/23	1981–1999	MA	OS	0.617 (0.252–1.514)	NS	8	GLUT1, cerbB-2, stage, diagnosis, sex, age
Dong et al. (2016)	China	R	Breast cancer	68/121	2003–2009	UA	OS	0.36 (0.26–0.49)	Poor	7	NR

Table 5 Correlation between glycolytic transcriptional regulators and glycolytic proteins in this analysis

Reference	Country	Study design	Cancer types	Glycolytic proteins	Recruitment time	Conclusion
HIF-1α						
Kolev et al. (2008)	Japan	R	Gastric carcinoma	LDH5	1992–1999	Positive
Qiu et al. (2011)	China	R	Gastric carcinoma	HK-II	1999–2001	Positive
Andersen et al. (2011)	Norway	R	Squamous cell lung cancer	GLUT1	1990–2004	Negative
Kwon et al. (2013)	Korea	R	Phyllodes tumors	GLUT1	2000–2010	Positive
Kim et al. (2013)	Korea	R	Cervical cancer	GLUT1	1996–2010	Positive
Berlth et al. (2015)	Germany	R	Gastric Adenocarcinoma	GLUT1	1996–2007	Positive
Goos et al. (2016)	Dutch	R	Colorectal cancer	GLUT1	1990–2010	Positive
Starska et al. (2015)	Poland	R	Laryngeal cancer	GLUT1	2003–2011	Positive
Swartz et al. (2016)	Netherland	R	Oropharyngeal squamous cell carcinomas	GLUT1	1997–2011	Negative
Boström et al. (2016)	Canada	R	Bladder cancer	GLUT1	NR	Negative
Boström et al. (2016)	Finland	R	Bladder cancer	GLUT1	NR	Negative
P53						
Kim et al. (2002)	Korea	R	Gallbladder cancer	GLUT1	1981–1999	Negative
Kang et al. (2002)	Korea	R	Breast cancer	GLUT1	1996–1997	Negative
Sung et al. (2010)	Korea	R	Ampulla of vater cancer	GLUT1	1983–2007	Negative
Sung et al. (2010)	Korea	R	Pancreatic cancer	GLUT1	1983–2007	Negative
Sung et al. (2010)	Korea	R	Extrahepatic bile duct cancer	GLUT1	1983–2007	Negative
Sung et al. (2010)	Korea	R	Gallbladder cancer	GLUT1	1983–2007	Negative
Dong et al. (2016)	China	R	Breast cancer	Glc6PDH	2003–2009	Positive

heterogeneity. Sensitivity analysis was performed by sequentially omitting each study. For the meta-analyses between prognosis and glycolysis-related proteins, the pooled HR and 95% CI were not obviously influenced by removing any single study in OS (Fig. 4a). But the result of sensitivity analysis indicated that the study published by Sebastiani et al. (2004) in DFS and Karachaliou et al. (2013) in PFS significantly influenced the pooled HR (Fig. 4b, c). After excluding the studies by Sebastiani et al. (2004) and Karachaliou et al. (2013), the meta-analyses of the remaining studies were stable. The pooled HRs for DFS changed from 2.27 (95% CI 1.72–2.99, $P < 0.001$) to 2.40 (95% CI 1.84–3.13, $P < 0.001$), and the pooled HR for PFS altered from 2.48 (95% CI 1.66–3.70, $P < 0.001$) to 2.79 (95% CI 2.22–3.51, $P < 0.001$). For the meta-analyses between clinicopathological features and glycolysis-related proteins, the results were similar after the sequential exclusion of each study, which suggested the stability of meta-analyses (Fig. 4d–k).

Publication bias

Begg's test, Egger's test and funnel plot were conducted to estimate the publication bias of the included studies. For the correlation between prognosis and glycolysis-related proteins, the results of Begg's test and the shape of funnel plot presented us with no significant publication bias for OS ($P = 0.246$), DFS ($P = 0.284$), and PFS ($P = 1.000$) (Fig. 5a–c). Further Egger's tests showed the similar result. As to the correlation between clinicopathological features and glycolysis-related proteins, no evidence of publication bias for other meta-analyses was observed except for lymph node metastasis ($P = 0.007$) (Fig. 5d–k). For the correlation between prognosis and the key glycolytic transcriptional regulators, no evidence of publication bias was observed (Supplemental Figs. 3A, B, 4).

Discussion

The phenomenon, increased glucose uptake in cancer cells in normoxic condition, was originally found by Otto Warburg and have been clinically exploited to detect tumor cells by positron-emission tomography (PET). Evidence suggested that overexpression of glycolytic enzymes significantly associated with high 18F-FDG uptake (Fong et al. 1999; Lubezky et al. 2007; Brito et al. 2015; Cho et al. 2015; Cavalcante et al. 2016). Metabolic genes, especially glycolytic genes, held immense potential as ideal biomarkers for diagnosis and prognosis in tumors. Quite a few studies were carried out to assess the probability. However, inconsistent results were found in different studies (Baer et al. 2002; Koukourakis et al. 2003, 2006, 2009; Giatromanolaki et al.

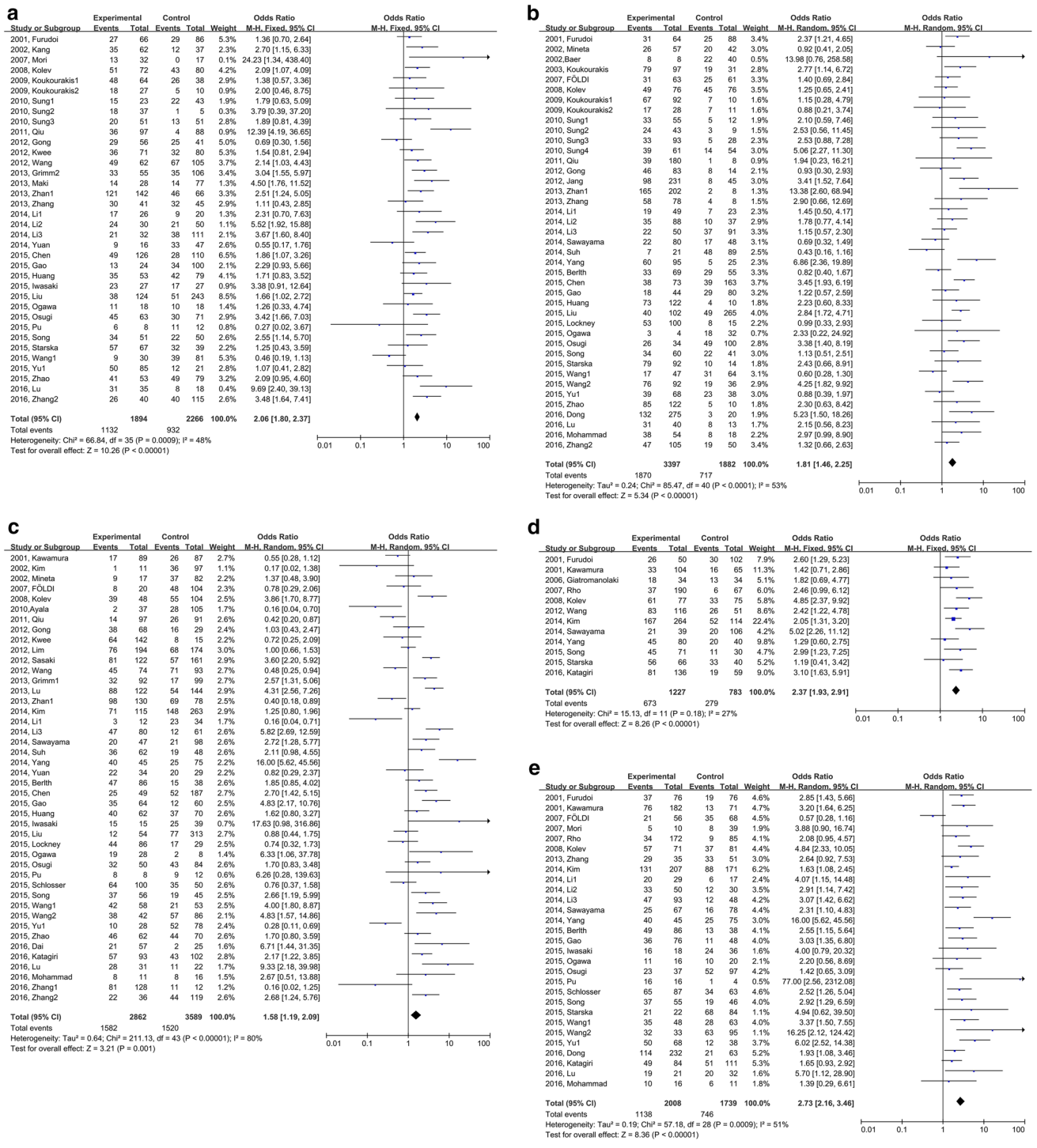


Fig. 3 Forest plot of hazard ratio (HR) for the association between glycolysis-related proteins and clinicopathological features: large tumor size (**a**), poor differentiated tumors (**b**), advanced tumor stage (**c**), deeper invasion (**d**), positive lymph node metastasis (**e**), positive vascular invasion (**f**), male gender (**g**), elder patients (**h**)

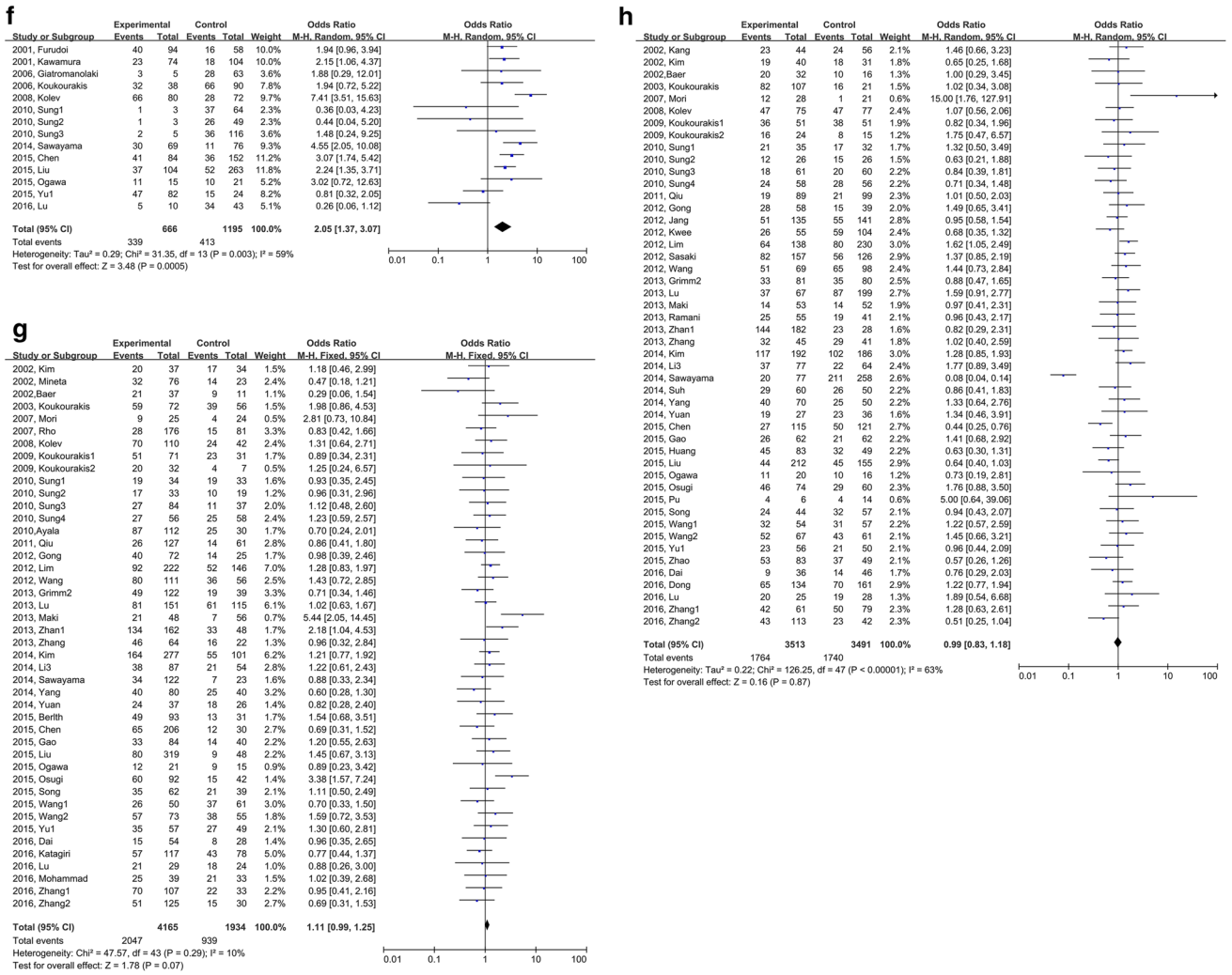


Fig. 3 (continued)

2006; Foldi et al. 2007; Rho et al. 2007; Kolev et al. 2008; Zhou et al. 2008; Ayala et al. 2010; Benesch et al. 2010; Danner et al. 2010; Kayser et al. 2010; Zhuang et al. 2010; Qiu et al. 2011; Fritz et al. 2012; Gong et al. 2012; Kwee et al. 2012; Lim et al. 2012; Wang et al. 2012, 2015a, b; Grimm et al. 2013a, b; Hjerpe et al. 2013; Karachaliou et al. 2013; Kim et al. 2002, 2013, 2014; Lu et al. 2013, 2016; Sato-Tadano et al. 2013; Zhan et al. 2013; Zhang et al. 2013, 2016a, b; Li et al. 2014a, b; Suh et al. 2014; Yang et al. 2014; Yuan et al. 2014; Chen et al. 2015; Gao et al. 2015; Hu et al. 2015; Huang et al. 2015; Liu et al. 2015; Lockney et al. 2015; Ogawa et al. 2015; Pu et al. 2015; Song et al. 2015; Yu et al. 2015a, b; Zhao et al. 2015; Dai et al. 2016; Dong et al. 2016; Katagiri et al. 2016; Mohammad et al. 2016; Schlosser et al. 2017; Furudoi et al. 2001; Kawamura et al. 2001; Kang et al. 2002; Mineta et al. 2002; Hoskin et al. 2003; Sebastiani 2004; Lyshchik et al. 2007; Mori et al. 2007; Fenske et al. 2009; Sung et al. 2010; Andersen et al. 2011; Kitamura et al. 2011; Jang et al. 2012; Sasaki et al. 2012; Cho et al. 2013; Kwon et al. 2013; Maki et al. 2013; Ramani et al. 2013; Sawayama et al. 2014; Berlth et al. 2015; Iwasaki et al. 2015; Osugi et al. 2015; Starska et al. 2015; Bostrom et al. 2016; Goos et al. 2016; Swartz et al. 2016; Yan et al. 2016).

Our meta-analysis demonstrated that glycolysis-related proteins is significantly associated with biologically aggressive phenotypes such as larger tumor size, poor tumor differentiation, advanced tumor stage, deeper invasion, positive lymph node metastasis and positive vascular invasion. The results demonstrated that increased glycolysis was significantly linked with poor prognosis. Notably, we found that a significant link between glycolysis-related proteins and overall survival existed in cancers of the digestive system, including colorectal cancer, gallbladder cancer, bile duct cancer, esophageal cancer, hepatocellular cancer and pancreatic cancer. Subsequent pooled results

Table 6 Stratified analysis for DFS

Stratified analysis	Number of studies	Number of patients	Pooled HR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	*P* value
Antibodies						
GLUT1	10	1785	1.97 (1.33–2.91)	0.001	62	0.002
HKII	2	313	2.55 (1.49–4.73)	0.001	0.0	0.920
LDH5	4	814	3.84 (1.19–12.35)	0.02	89	0.000
PYK-M2	3	858	2.13 (1.35–3.37)	0.001	57	0.100
Study location						
Asian	14	3380	1.86 (1.54–2.23)	0.000	15	0.290
Europe	5	819	2.93 (1.23–6.99)	0.020	92	0.000
Sample size						
> 100	19	4210	2.23 (1.67–2.98)	0.000	75	0.000
< 100	2	181	2.86 (1.60–5.11)	0.000	0.0	0.910
Categories of diseases						
Gastric cancer	3	1151	1.62 (1.21–2.17)	0.001	12	0.320
Breast cancer	3	728	1.98 (1.15–3.40)	0.010	0.0	0.610
Quality of studies						
High quality	16	3625	2.53 (1.83–3.49)	0.000	70	0.000
Moderate quality	5	766	1.52 (1.01–2.27)	0.040	57	0.050

Table 7 Stratified analysis for PFS

Stratified analysis	Number of studies	Number of patients	Pooled HR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	*P* value
Antibodies						
HKII	2	382	2.96 (1.96–4.48)	0.001	0.0	0.730
PYK-M2	2	359	1.88 (0.95–3.72)	0.070	90	0.002
Sample size						
> 100	4	677	2.74 (2.18–3.46)	0.000	0.0	0.850
< 100	3	139	2.64 (0.60–11.74)	0.200	53	0.120
Categories of diseases						
Cervical cancer	2	187	2.91 (1.56–5.46)	0.001	0.0	0.890
Breast cancer	2	315	4.06 (1.00–16.55)	0.050	51	0.150

showed that there was a significant association between glycolysis-related proteins and DFS as well as PFS.

Results above showed that higher activated glycolysis was obviously correlated with poor prognosis. Accumulating data supported that increased metabolic activity and glucose consumption had been linked to tumor aggressiveness. The incorporation of molecular assessment has become part of routine practice for therapeutic stratification, current treatment algorithms for most of cancers still depend on only imaging and histological assessments to guide treatment and help classify prognosis. It is beneficial to stratify patients and to develop subgroup-specific therapies. Moreover, glycolysis was independent of intact mitochondrial function, which was reported dysfunction in some cancer cells (Zhang et al. 2013a, b). During the process of glycolysis, glucose was converted into lactate whose export subsequently created an acidic extracellular environment. Acidification of the cellular matrix by lactate production during glycolysis was probably one of the main factors that accelerated cancer aggressiveness (Stubbs et al. 2000). Therefore, it may be the reason that why glycolytic status was significantly associated with biologically aggressive phenotypes.

In subgroup analysis, we found that significant link between glycolysis-related proteins and overall survival existed in cancers of digestive system. Significant link also existed in relation between overall survival and glycolysis-related proteins in breast cancer and nasopharyngeal carcinoma. However, there was no significant association between prognosis and glycolysis-related proteins in lung cancer, ovarian cancer, and melanoma. Due to insufficient data in ovarian cancer and melanoma, the association between prognosis and glycolysis-related proteins was still obscure and the results should be taken into careful consideration. As for

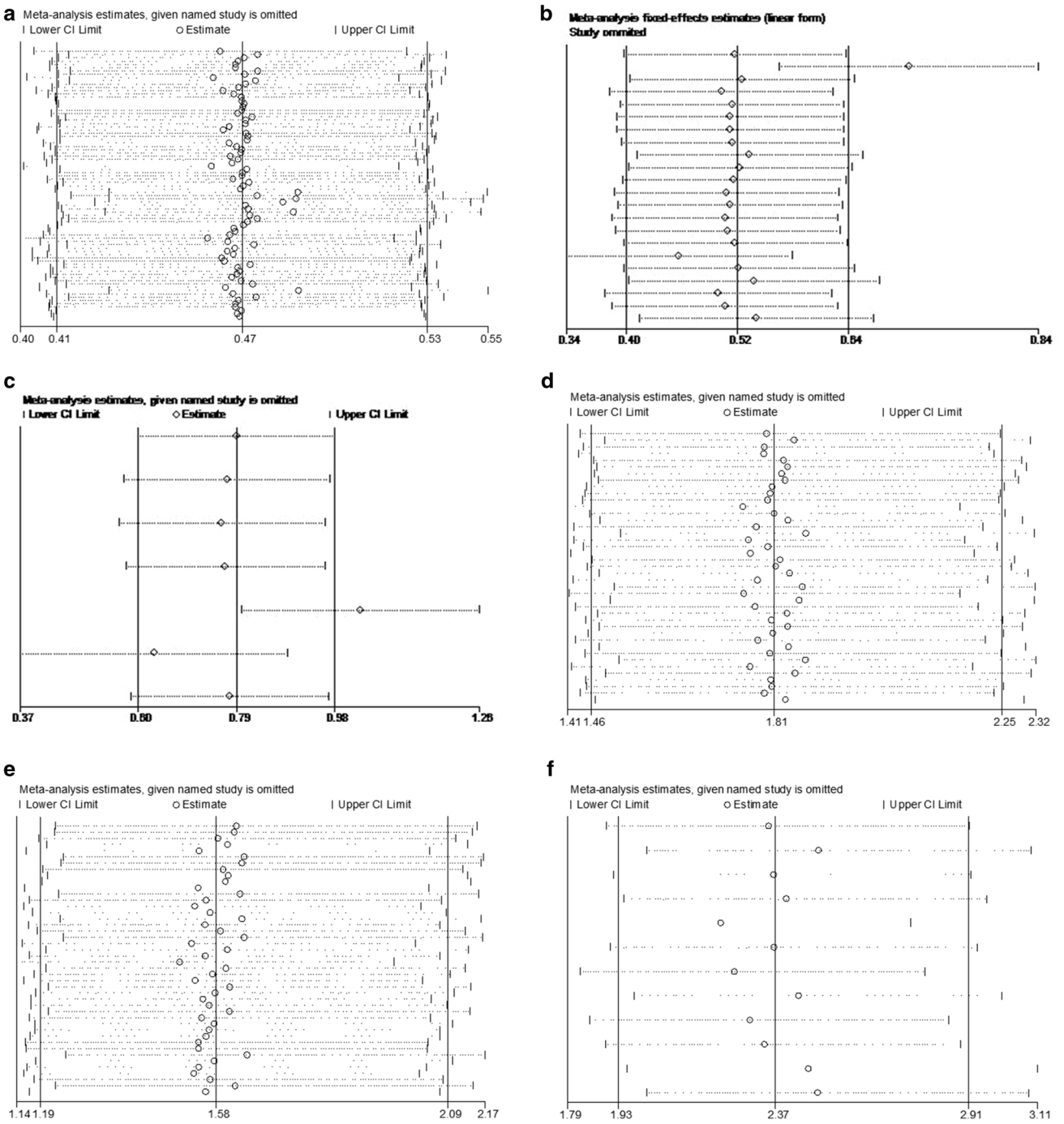
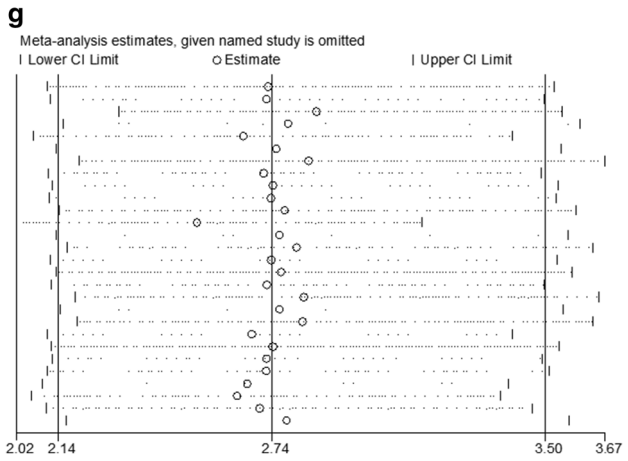
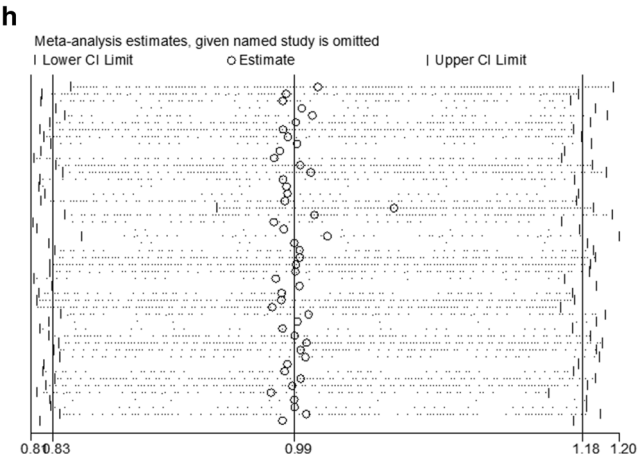


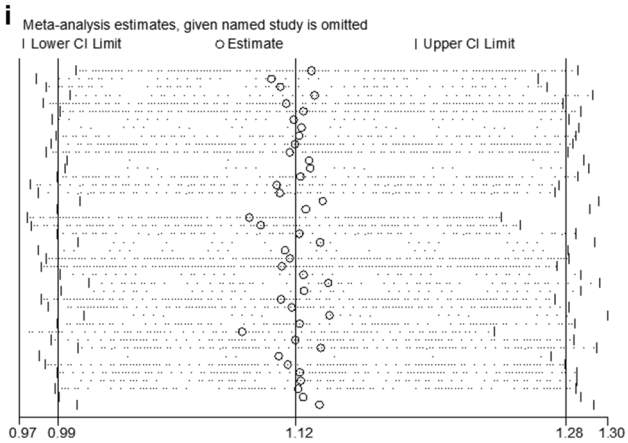
Fig. 4 Sensitivity analysis was performed in present studies for glycolysis-related proteins. **a** OS; **b** DFS; **c** PFS; **d** tumor grade; **e** tumor stage; **f** depth of invasion; **g** lymph node metastasis; **h** age; **i** gender; **j** vascular invasion; **k** tumor size

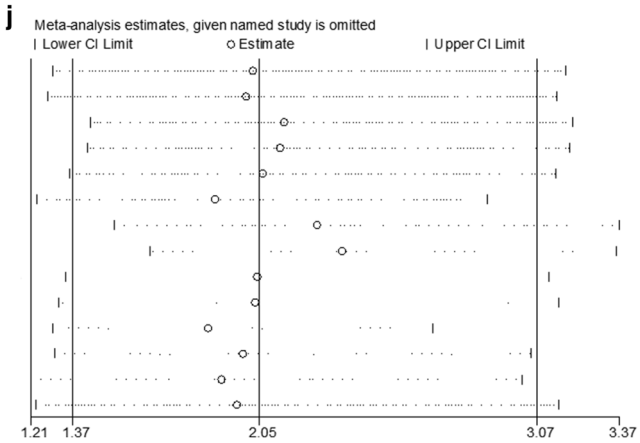
lung cancer, there were several subtypes of lung cancer and the prognosis differed significantly among subtypes of lung cancer. Therefore, the association between glycolysis-related proteins and lung cancer is still unclear.

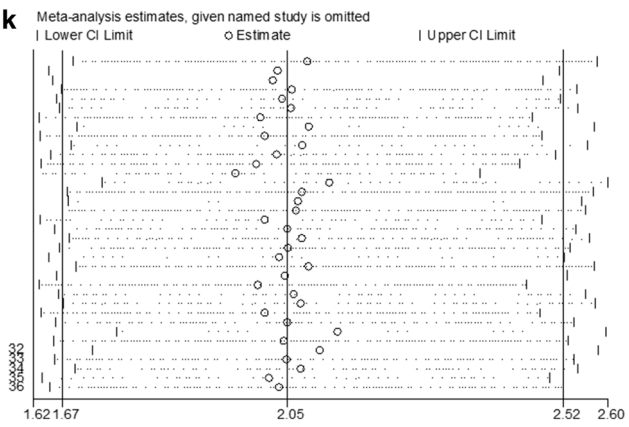
In the included studies, significant correlation was found between Glc6PDH and p53. HIF-1α was found to have a significant correlation with LDH5 and HKII, and some studies found that HIF-1α has a significant correlation with GLUT1. The association between prognosis and key glycolytic transcriptional regulators was analyzed in parallel to the glycolysis-related proteins with the data from the included studies. And we found that high-level expression of HIF-1α and mutation of p53 was significantly associated with shorter overall survival which has the same conclusion with











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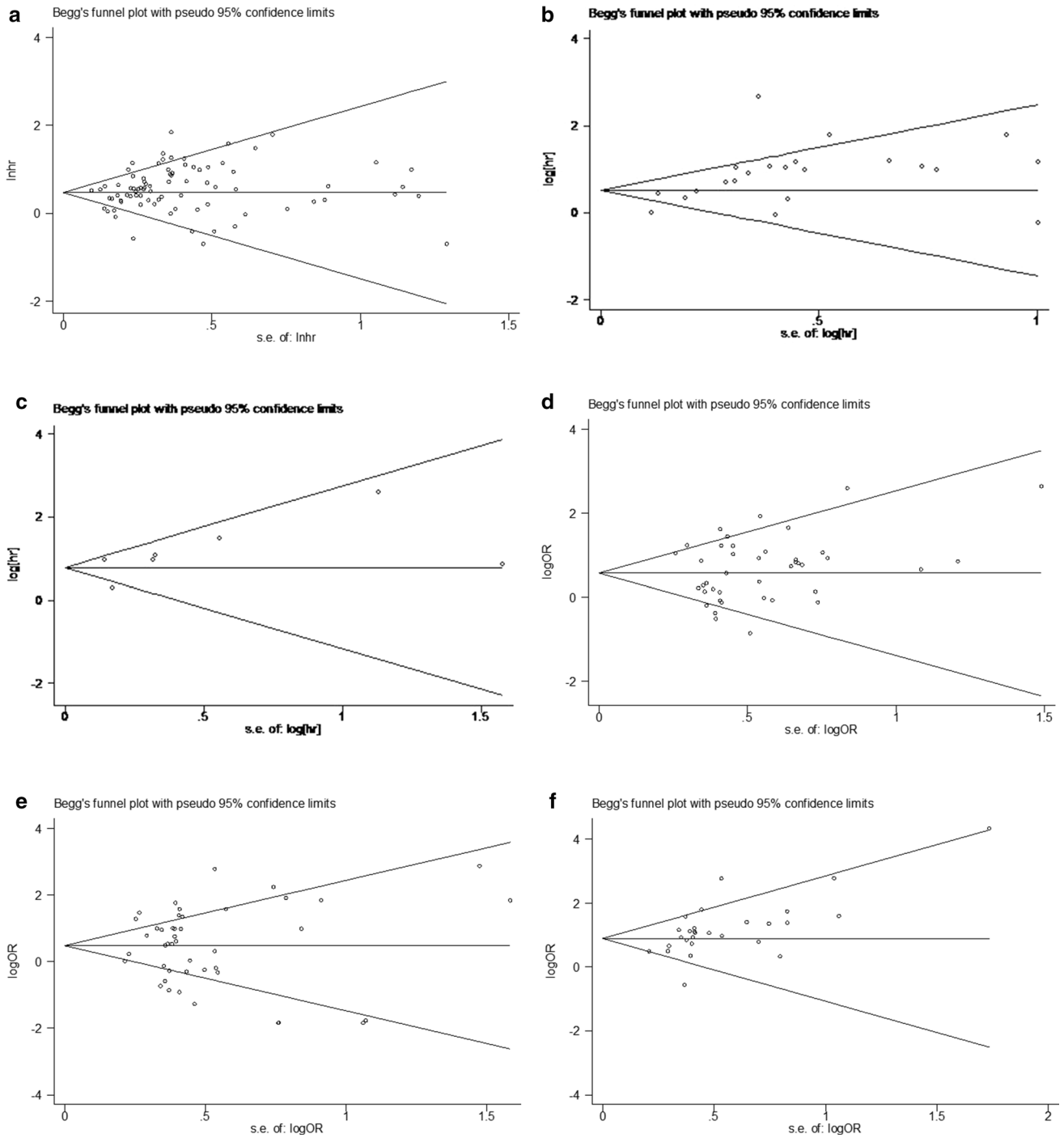
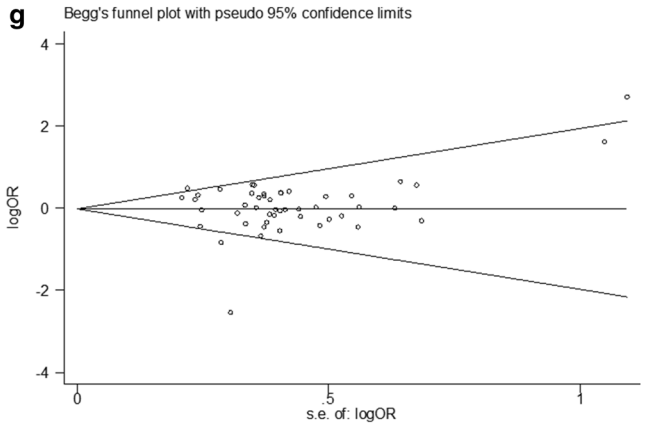
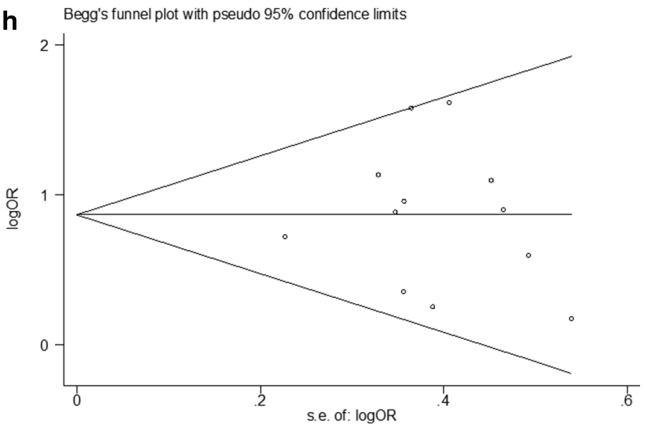
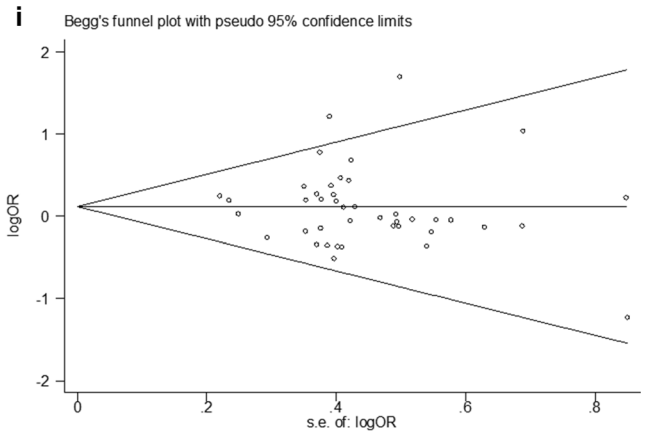
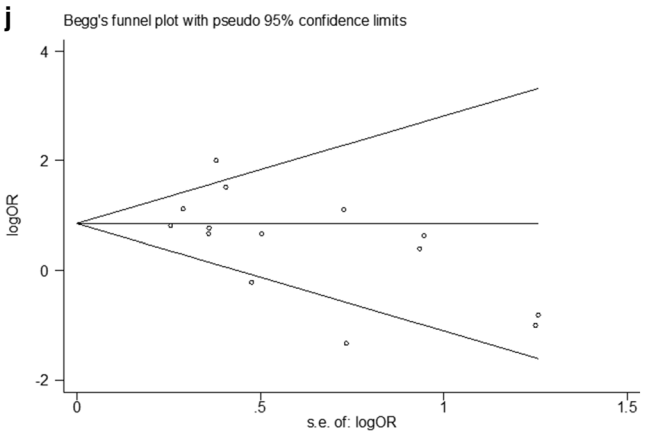


Fig. 5 Begg's funnel plot for the assessment of publication bias in the present study for glycolysis-related proteins. **a** OS; **b** DFS; **c** PFS; **d** tumor grade; **e** tumor stage; **f** lymph node metastasis; **g** age; **h** depth of invasion; **i** gender; **j** vascular invasion; **k** tumor size









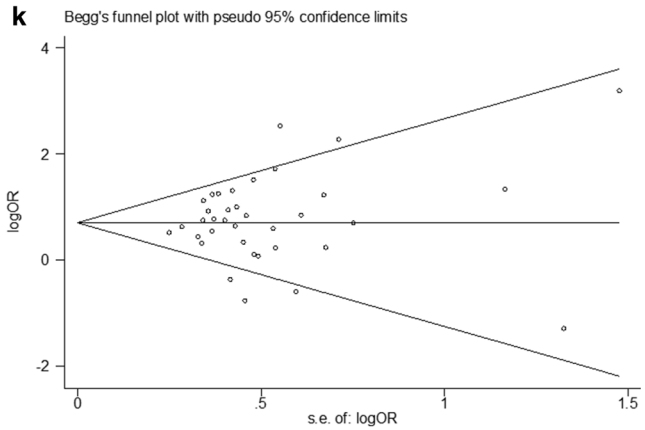


Fig. 5 (continued)

Table 8 Drugs in development in patients with cancer in glycolysis (http://www.clinicaltrials.gov)

Targets	Corresponding chemicals	Development stage	Trial ID number	Cancer types
GLUTs	Resveratrol	Phase 1	NCT00256334	Colon cancer
		Phase 1/Phase 2	NCT02261844	Liver cancer
		Phase 1	NCT00098969	Unspecified adult solid tumor
HKII	2-Deoxyglucose	Phase 1/Phase 2	NCT00633087	Prostate cancer
		Phase 1	NCT00247403	Intracranial neoplasms, neoplasm metastasis
		Phase 1	NCT00096707	Lung cancer, breast cancer, pancreatic cancer, head and neck cancer, gastric cancer
		Phase 2	NCT00001568	Colorectal neoplasm
		Phase 3	NCT00435448	Prostate cancer
	Resveratrol	Phase 1	NCT00256334	Colon cancer
		Phase 1/Phase 2	NCT02261844	Liver cancer
		Phase 1	NCT00098969	Unspecified adult solid tumor
PFK	Sulforaphane	Phase 2	NCT01228084	Adenocarcinoma of the prostate, recurrent prostate cancer
		Phase 2	NCT00982319	Breast cancer
PK	siRNA	Phase 1	NCT01591356	Advanced cancers
MCT1	AZD3965	Phase 1	NCT01791595	Adult solid tumor, prostate cancer, gastric cancer, diffuse large B-cell lymphoma
PDK	Dichloroacetate	Phase 2	NCT01029925	Metastatic breast cancer
		Phase 2	NCT01386632	Squamous cell carcinoma of the head and neck
		Phase 1	NCT01111097	Brain tumor, glioblastoma
		Phase 1	NCT00566410	Neoplasms

glycolysis-related proteins. These results provide a more solid support that glycolysis-related proteins were regulated by key glycolytic transcriptional regulators and played important roles in glycolysis which can be used as predictors for survival in cancers. Recently, there has been growing interest in understanding cancer altered metabolism and targeting cancer metabolism holds a promising strategy for cancer treatment. Evidence showed that inhibition of these proteins in cancer cells obviously disrupted cancer cell proliferation, invasion, and reduced chemoresistance (Hamanaka and Chandel 2012; Galluzzi et al. 2013; Son et al. 2013). As glycolysis is vital for tumor cell metabolism and have prognostic potential in a variety of tumors, targeting glycolysis-related markers is an effective node of pharmacological interference against tumor metabolism. However, these proteins are also involved in crucial processes, targeting these proteins with inhibitors may also interfere biological behavior in normal cells. Therefore, it is a challenging problem to develop and implement increasingly specific inhibitors that can distinguish cancerous from normal cells. To date, as reported in Table 8, some attempts have been made and some molecular targets in glycolysis have shown their potential value in the cancer therapy. Several small molecules, as a single agent or in combination with other therapeutic modalities, exhibit promising anticancer activity. Anyway, it needs further studies to find more effective targeted anti-tumor agents and its mechanisms. Taken together, these targeting glycolysis-related inhibitors may be widely applied in treatment of most human cancers according to findings in present study.

However, limitations of this meta-analysis should also be discussed as they may affect the interpretation of the results. Some limitations of our meta-analysis should be acknowledged. First, only papers published in English were included, which probably introduced bias. Second, there was no united IHC evaluation and cutoff point in this field currently. The evaluation of GLUT1 expression and determination of cutoff values were varied across studies. Since no standardized techniques and scores to assess expression of glycolysis-related proteins are available in cancers, inconsistency in methodology may be an issue. Third, different methods of survival data analysis in different studies should be considered a potential source of heterogeneity. Although most studies adjusted their HRs and 95% CIs using multivariate analysis, variables added into Cox proportional hazard models were different from study to study. Finally, these findings were all based on studies with retrospective de sign studies, which would also reduce the statistic power.

Conclusion

To sum up, our study indicated that glycolytic transcriptional regulators and glycolysis-related proteins in cancers were significantly associated with poor prognosis, which suggested that glycolytic transcriptional regulators and

glycolysis-related proteins may be potential valuable prognostic biomarkers for various cancers, especially in cancers of digestive system. The results also showed that glycolysis-related proteins was significantly associated with biologically aggressive phenotypes, which suggests that glycolysis is probably one of the main factors that drives cancer aggressiveness. However, glycolysis is a complex, multistep, and highly dynamic process; the association between glycolytic status and tumor aggressiveness, metastasis, and patient survival is still reliant on future validation. Therefore, further studies, both epidemiological and experimental, are warranted to clarify the association between glycolytic status and prognosis of cancer patients.

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Compliance with ethical standards

Conflict of interest This study was funded by the above institutions and has received research grants from it. All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

Andersen S, Eilertsen M, Donnem T, Al-Shibli K, Al-Saad S et al (2011) Diverging prognostic impacts of hypoxic markers according to NSCLC histology. Lung Cancer 72:294–302

Ashrafian H (2006) Cancer's sweet tooth: the Janus effect of glucose metabolism in tumorigenesis. Lancet 367:618–621

Ayala FR, Rocha RM, Carvalho KC, Carvalho AL, da Cunha IW et al (2010) GLUT1 and GLUT3 as potential prognostic markers for oral squamous cell carcinoma. Molecules 15:2374–2387

Baer S, Casaubon L, Schwartz MR, Marcogliese A, Younes M (2002) Glut3 expression in biopsy specimens of laryngeal carcinoma is associated with poor survival. Laryngoscope 112:393–396

Benesch C, Schneider C, Voelker HU, Kapp M, Caffier H et al (2010) The clinicopathological and prognostic relevance of pyruvate kinase M2 and pAkt expression in breast cancer. Anticancer Res 30:1689–1694

Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K et al (2006) TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell 126:107–120

Bensinger SJ, Christofk HR (2012) New aspects of the Warburg effect in cancer cell biology. Semin Cell Dev Biol 23:352–361

Bentz S, Cee A, Endlicher E, Wojtal KA, Naami A et al (2013) Hypoxia induces the expression of transketolase-like 1 in human colorectal cancer. Digestion 88:182–192

Berlth F, Monig S, Pinther B, Grimminger P, Maus M et al (2015) Both GLUT-1 and GLUT-14 are independent prognostic factors in gastric adenocarcinoma. Ann Surg Oncol 22(Suppl 3):S822–S831

Bostrom PJ, Thoms J, Sykes J, Ahmed O, Evans A et al (2016) Hypoxia marker GLUT-1 (glucose transporter 1) is an independent prognostic factor for survival in bladder cancer patients treated with radical cystectomy. Bladder Cancer 2:101–109

Brito AF, Abrantes AM, Ribeiro M, Oliveira R, Casalta-Lopes J et al (2015) Fluorine-18 fluorodeoxyglucose uptake in hepatocellular carcinoma: correlation with glucose transporters and p53 expression. J Clin Exp Hepatol 5:183–189

Cavalcante IP, Zerbini MC, Alencar GA, Mariani Bde P, Buchpiguel CA et al (2016) High 18F-FDG uptake in PMAH correlated with normal expression of Glut1, HK1, HK2, and HK3. Acta Radiol 57:370–377

Chen Z, Lu X, Wang Z, Jin G, Wang Q et al (2015) Co-expression of PKM2 and TRIM35 predicts survival and recurrence in hepatocellular carcinoma. Oncotarget 6:2538–2548

Cho H, Lee YS, Kim J, Chung JY, Kim JH (2013) Overexpression of glucose transporter-1 (GLUT-1) predicts poor prognosis in epithelial ovarian cancer. Cancer Invest 31:607–615

Cho MH, Park CK, Park M, Kim WK, Cho A et al (2015) Clinicopathologic features and molecular characteristics of glucose metabolism contributing to (1)(8)F-fluorodeoxyglucose uptake in gastrointestinal stromal tumors. PLoS One 10:e0141413

Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE et al (2008a) The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature 452:230–233

Christofk HR, Vander Heiden MG, Wu N, Asara JM, Cantley LC (2008b) Pyruvate kinase M2 is a phosphotyrosine-binding protein. Nature 452:181–186

Contractor T, Harris CR (2012) p53 negatively regulates transcription of the pyruvate dehydrogenase kinase Pdk2. Cancer Res 72:560–567

Dai Z, Pan S, Chen C, Cao L, Li X et al (2016) Down-regulation of succinate dehydrogenase subunit B and up-regulation of pyruvate dehydrogenase kinase 1 predicts poor prognosis in recurrent nasopharyngeal carcinoma. Tumour Biol 37:5145–5152

Danner BC, Didilis VN, Wiemeyer S, Stojanovic T, Kitz J et al (2010) Long-term survival is linked to serum LDH and partly to tumour LDH-5 in NSCLC. Anticancer Res 30:1347–1351

Dong T, Kang X, Liu Z, Zhao S, Ma W et al (2016) Altered glycometabolism affects both clinical features and prognosis of triple-negative and neoadjuvant chemotherapy-treated breast cancer. Tumour Biol 37:8159–8168

Elson DA, Ryan HE, Snow JW, Johnson R, Arbeit JM (2000) Coordinate up-regulation of hypoxia inducible factor (HIF)-1alpha and HIF-1 target genes during multi-stage epidermal carcinogenesis and wound healing. Cancer Res 60:6189–6195

Fenske W, Volker HU, Adam P, Hahner S, Johanssen S et al (2009) Glucose transporter GLUT1 expression is an stage-independent predictor of clinical outcome in adrenocortical carcinoma. Endocr Relat Cancer 16:919–928

Foldi M, Stickeler E, Bau L, Kretz O, Watermann D et al (2007) Transketolase protein TKTL1 overexpression: a potential biomarker and therapeutic target in breast cancer. Oncol Rep 17:841–845

Fong Y, Saldinger PF, Akhurst T, Macapinlac H, Yeung H et al (1999) Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. Am J Surg 178:282–287

Fritz P, Coy JF, Murdter TE, Ott G, Alscher MD et al (2012) TKTL-1 expression in lung cancer. Pathol Res Pract 208:203–209

Furudoi A, Tanaka S, Haruma K, Yoshihara M, Sumii K et al (2001) Clinical significance of human erythrocyte glucose transporter 1 expression at the deepest invasive site of advanced colorectal carcinoma. Oncology 60:162–169

Furuta E, Okuda H, Kobayashi A, Watabe K (2010) Metabolic genes in cancer: their roles in tumor progression and clinical implications. Biochim Biophys Acta 1805:141–152

Galluzzi L, Kepp O, Vander Heiden MG, Kroemer G (2013) Metabolic targets for cancer therapy. Nat Rev Drug Discov 12:829–846

Gao Y, Xu D, Yu G, Liang J (2015) Overexpression of metabolic markers HK1 and PKM2 contributes to lymphatic metastasis and adverse prognosis in Chinese gastric cancer. Int J Clin Exp Pathol 8:9264–9271

Giatromanolaki A, Sivridis E, Gatter KC, Turley H, Harris AL et al (2006) Lactate dehydrogenase 5 (LDH-5) expression in endometrial cancer relates to the activated VEGF/VEGFR2(KDR) pathway and prognosis. Gynecol Oncol 103:912–918

Gong L, Cui Z, Chen P, Han H, Peng J et al (2012) Reduced survival of patients with hepatocellular carcinoma expressing hexokinase II. Med Oncol 29:909–914

Goos JA, de Cuba EM, Coupe VM, Diosdado B, Delis-Van Diemen PM et al (2016) Glucose transporter 1 (SLC2A1) and vascular endothelial growth factor A (VEGFA) predict survival after resection of colorectal cancer liver metastasis. Ann Surg 263:138–145

Gottlieb E (2011) p53 guards the metabolic pathway less travelled. Nat Cell Biol 13:195–197

Grimm M, Alexander D, Munz A, Hoffmann J, Reinert S (2013a) Increased LDH5 expression is associated with lymph node metastasis and outcome in oral squamous cell carcinoma. Clin Exp Metastasis 30:529–540

Grimm M, Schmitt S, Teriete P, Biegner T, Stenzl A et al (2013b) A biomarker based detection and characterization of carcinomas exploiting two fundamental biophysical mechanisms in mammalian cells. BMC Cancer 13:569

Hamanaka RB, Chandel NS (2012) Targeting glucose metabolism for cancer therapy. J Exp Med 209:211–215

Hjerpe E, Egyhazi Brage S, Carlson J, Frostvik Stolt M, Schedvins K et al (2013) Metabolic markers GAPDH, PKM2, ATP5B and BEC-index in advanced serous ovarian cancer. BMC Clin Pathol 13:30

Ho HY, Cheng ML, Chiu DT (2007) Glucose-6-phosphate dehydrogenase—from oxidative stress to cellular functions and degenerative diseases. Redox Rep 12:109–118

Hoskin PJ, Sibtain A, Daley FM, Wilson GD (2003) GLUT1 and CAIX as intrinsic markers of hypoxia in bladder cancer: relationship with vascularity and proliferation as predictors of outcome of ARCON. Br J Cancer 89:1290–1297

Hu W, Lu SX, Li M, Zhang C, Liu LL et al (2015) Pyruvate kinase M2 prevents apoptosis via modulating Bim stability and associates with poor outcome in hepatocellular carcinoma. Oncotarget 6:6570–6583

Huang X, Liu M, Sun H, Wang F, Xie X et al (2015) HK2 is a radiation resistant and independent negative prognostic factor for patients with locally advanced cervical squamous cell carcinoma. Int J Clin Exp Pathol 8:4054–4063

Iwasaki K, Yabushita H, Ueno T, Wakatsuki A (2015) Role of hypoxia-inducible factor-1alpha, carbonic anhydrase-IX, glucose transporter-1 and vascular endothelial growth factor associated with lymph node metastasis and recurrence in patients with locally advanced cervical cancer. Oncol Lett 10:1970–1978

Jang SM, Han H, Jang KS, Jun YJ, Jang SH et al (2012) The glycolytic phenotype is correlated with aggressiveness and poor prognosis in invasive ductal carcinomas. J Breast Cancer 15:172–180

Kallinowski F, Schlenger KH, Runkel S, Kloes M, Stohrer M et al (1989) Blood flow, metabolism, cellular microenvironment, and growth rate of human tumor xenografts. Cancer Res 49:3759–3764

Kang SS, Chun YK, Hur MH, Lee HK, Kim YJ et al (2002) Clinical significance of glucose transporter 1 (GLUT1) expression in human breast carcinoma. Jpn J Cancer Res 93:1123–1128

Karachaliou N, Papadaki C, Lagoudaki E, Trypaki M, Sfakianaki M et al (2013) Predictive value of BRCA1, ERCC1, ATP7B, PKM2, TOPOI, TOPOmicron-IIA, TOPOIIB and C-MYC genes in patients with small cell lung cancer (SCLC) who received first line therapy with cisplatin and etoposide. PLoS One 8:e74611

Katagiri M, Karasawa H, Takagi K, Nakayama S, Yabuuchi S et al (2016) Hexokinase 2 in colorectal cancer: a potent prognostic factor associated with glycolysis, proliferation and migration. Histol Histopathol 2016:11799

Kawamura T, Kusakabe T, Sugino T, Watanabe K, Fukuda T et al (2001) Expression of glucose transporter-1 in human gastric carcinoma: association with tumor aggressiveness, metastasis, and patient survival. Cancer 92:634–641

Kayser G, Kassem A, Sienel W, Schulte-Uentrop L, Mattern D et al (2010) Lactate-dehydrogenase 5 is overexpressed in non-small cell lung cancer and correlates with the expression of the transketolase-like protein 1. Diagn Pathol 5:22

Kim YW, Park YK, Yoon TY, Lee SM (2002) Expression of the GLUT1 glucose transporter in gallbladder carcinomas. Hepatogastroenterology 49:907–911

Kim BW, Cho H, Chung JY, Conway C, Ylaya K et al (2013a) Prognostic assessment of hypoxia and metabolic markers in cervical cancer using automated digital image analysis of immunohistochemistry. J Transl Med 11:185

Kim JG, Lee SJ, Chae YS, Kang BW, Lee YJ et al (2013b) Association between phosphorylated AMP-activated protein kinase and MAPK3/1 expression and prognosis for patients with gastric cancer. Oncology 85:78–85

Kim HS, Lee HE, Yang HK, Kim WH (2014) High lactate dehydrogenase 5 expression correlates with high tumoral and stromal vascular endothelial growth factor expression in gastric cancer. Pathobiology 81:78–85

Kitamura K, Hatano E, Higashi T, Narita M, Seo S et al (2011) Proliferative activity in hepatocellular carcinoma is closely correlated with glucose metabolism but not angiogenesis. J Hepatol 55:846–857

Kolev Y, Uetake H, Takagi Y, Sugihara K (2008) Lactate dehydrogenase-5 (LDH-5) expression in human gastric cancer: association with hypoxia-inducible factor (HIF-1alpha) pathway, angiogenic factors production and poor prognosis. Ann Surg Oncol 15:2336–2344

Koukourakis MI, Giatromanolaki A, Sivridis E, Bougioukas G, Didilis V et al (2003) Lactate dehydrogenase-5 (LDH-5) overexpression in non-small-cell lung cancer tissues is linked to tumour hypoxia, angiogenic factor production and poor prognosis. Br J Cancer 89:877–885

Koukourakis MI, Giatromanolaki A, Sivridis E, Gatter KC, Harris AL et al (2006) Lactate dehydrogenase 5 expression in operable colorectal cancer: strong association with survival and activated vascular endothelial growth factor pathway—a report of the Tumour Angiogenesis Research Group. J Clin Oncol 24:4301–4308

Koukourakis MI, Giatromanolaki A, Winter S, Leek R, Sivridis E et al (2009) Lactate dehydrogenase 5 expression in squamous cell head and neck cancer relates to prognosis following radical or postoperative radiotherapy. Oncology 77:285–292

Kuo W, Lin J, Tang TK (2000) Human glucose-6-phosphate dehydrogenase (G6PD) gene transforms NIH 3T3 cells and induces tumors in nude mice. Int J Cancer 85:857–864

Kwee SA, Hernandez B, Chan O, Wong L (2012) Choline kinase alpha and hexokinase-2 protein expression in hepatocellular carcinoma: association with survival. PLoS One 7:e46591

Kwon JE, Jung WH, Koo JS (2013) The expression of metabolism-related proteins in phyllodes tumors. Tumour Biol 34:115–124

Li W, Xu Z, Hong J, Xu Y (2014a) Expression patterns of three regulation enzymes in glycolysis in esophageal squamous cell carcinoma: association with survival. Med Oncol 31:118

Li J, Yang Z, Zou Q, Yuan Y, Li J et al (2014b) PKM2 and ACVR 1C are prognostic markers for poor prognosis of gallbladder cancer. Clin Transl Oncol 16:200–207

Lim JY, Yoon SO, Seol SY, Hong SW, Kim JW et al (2012) Overexpression of the M2 isoform of pyruvate kinase is an adverse prognostic factor for signet ring cell gastric cancer. World J Gastroenterol 18:4037–4043

Liu WR, Tian MX, Yang LX, Lin YL, Jin L et al (2015) PKM2 promotes metastasis by recruiting myeloid-derived suppressor cells and indicates poor prognosis for hepatocellular carcinoma. Oncotarget 6:846–861

Lockney NA, Zhang M, Lu Y, Sopha SC, Washington MK et al (2015) Pyruvate kinase muscle isoenzyme 2 (PKM2) expression is associated with overall survival in pancreatic ductal adenocarcinoma. J Gastrointest Cancer 46:390–398

Lu R, Jiang M, Chen Z, Xu X, Hu H et al (2013) Lactate dehydrogenase 5 expression in Non-Hodgkin lymphoma is associated with the induced hypoxia regulated protein and poor prognosis. PLoS One 8:e74853

Lu K, Yang J, Li DC, He SB, Zhu DM et al (2016) Expression and clinical significance of glucose transporter-1 in pancreatic cancer. Oncol Lett 12:243–249

Lubezky N, Metser U, Geva R, Nakache R, Shmueli E et al (2007) The role and limitations of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan and computerized tomography (CT) in restaging patients with hepatic colorectal metastases following neoadjuvant chemotherapy: comparison with operative and pathological findings. J Gastrointest Surg 11:472–478

Lum JJ, Bui T, Gruber M, Gordan JD, DeBerardinis RJ et al (2007) The transcription factor HIF-1alpha plays a critical role in the growth factor-dependent regulation of both aerobic and anaerobic glycolysis. Genes Dev 21:1037–1049

Lyshchik A, Higashi T, Hara T, Nakamoto Y, Fujimoto K et al (2007) Expression of glucose transporter-1, hexokinase-II, proliferating cell nuclear antigen and survival of patients with pancreatic cancer. Cancer Invest 25:154–162

Maki Y, Soh J, Ichimura K, Shien K, Furukawa M et al (2013) Impact of GLUT1 and Ki-67 expression on early stage lung adenocarcinoma diagnosed according to a new international multidisciplinary classification. Oncol Rep 29:133–140

Matoba S, Kang JG, Patino WD, Wragg A, Boehm M et al (2006) p53 regulates mitochondrial respiration. Science 312:1650–1653

McArdle S, Fallet R, Jeffries WB, Pettinger WA (1992) DOCA-enhanced sites of vasopressin-stimulated cAMP formation in rat cortical collecting tubule. Am J Physiol 263:F1093–F1097

Mineta H, Miura K, Takebayashi S, Misawa K, Araki K et al (2002) Prognostic value of glucose transporter 1 expression in patients with hypopharyngeal carcinoma. Anticancer Res 22:3489–3494

Mohammad GH, Olde Damink SW, Malago M, Dhar DK, Pereira SP (2016) Pyruvate kinase M2 and lactate dehydrogenase a are overexpressed in pancreatic cancer and correlate with poor outcome. PLoS One 11:e0151635

Mori Y, Tsukinoki K, Yasuda M, Miyazawa M, Kaneko A et al (2007) Glucose transporter type 1 expression are associated with poor prognosis in patients with salivary gland tumors. Oral Oncol 43:563–569

Ogawa H, Nagano H, Konno M, Eguchi H, Koseki J et al (2015) The combination of the expression of hexokinase 2 and pyruvate kinase M2 is a prognostic marker in patients with pancreatic cancer. Mol Clin Oncol 3:563–571

Osugi J, Yamaura T, Muto S, Okabe N, Matsumura Y et al (2015) Prognostic impact of the combination of glucose transporter 1 and ATP citrate lyase in node-negative patients with non-small lung cancer. Lung Cancer 88:310–318

Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834

Pauwels EK, Sturm EJ, Bombardieri E, Cleton FJ, Stokkel MP (2000) Positron-emission tomography with [18F]fluorodeoxyglucose. Part I. Biochemical uptake mechanism and its implication for clinical studies. J Cancer Res Clin Oncol 126:549–559

Pu H, Zhang Q, Zhao C, Shi L, Wang Y et al (2015) Overexpression of G6PD is associated with high risks of recurrent metastasis and poor progression-free survival in primary breast carcinoma. World J Surg Oncol 13:323

Qiu MZ, Han B, Luo HY, Zhou ZW, Wang ZQ et al (2011) Expressions of hypoxia-inducible factor-1alpha and hexokinase-II in gastric adenocarcinoma: the impact on prognosis and correlation to clinicopathologic features. Tumour Biol 32:159–166

Ramani P, Headford A, May MT (2013) GLUT1 protein expression correlates with unfavourable histologic category and high risk in patients with neuroblastic tumours. Virchows Arch 462:203–209

Rho M, Kim J, Jee CD, Lee YM, Lee HE et al (2007) Expression of type 2 hexokinase and mitochondria-related genes in gastric carcinoma tissues and cell lines. Anticancer Res 27:251–258

Sasaki H, Shitara M, Yokota K, Hikosaka Y, Moriyama S et al (2012) Overexpression of GLUT1 correlates with Kras mutations in lung carcinomas. Mol Med Rep 5:599–602

Sato-Tadano A, Suzuki T, Amari M, Takagi K, Miki Y et al (2013) Hexokinase II in breast carcinoma: a potent prognostic factor associated with hypoxia-inducible factor-1alpha and Ki-67. Cancer Sci 104:1380–1388

Sawayama H, Ishimoto T, Watanabe M, Yoshida N, Baba Y et al (2014) High expression of glucose transporter 1 on primary lesions of esophageal squamous cell carcinoma is associated with hematogenous recurrence. Ann Surg Oncol 21:1756–1762

Schlosser HA, Drebber U, Urbanski A, Haase S, Baltin C et al (2017) Glucose transporters 1, 3, 6, and 10 are expressed in gastric cancer and glucose transporter 3 is associated with UICC stage and survival. Gastric Cancer 20:83–91

Sebastiani V (2004) Fatty acid synthase is a marker of increased risk of recurrence in endometrial carcinoma. Gynecol Oncol 92:101–105

Son J, Lyssiotis CA, Ying H, Wang X, Hua S et al (2013) Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 496:101–105

Song Y, Liu D, He G (2015) TKTL1 and p63 are biomarkers for the poor prognosis of gastric cancer patients. Cancer Biomark 15:591–597

Starska K, Forma E, Jozwiak P, Brys M, Lewy-Trenda I et al (2015) Gene and protein expression of glucose transporter 1 and glucose transporter 3 in human laryngeal cancer-the relationship with regulatory hypoxia-inducible factor-1alpha expression, tumor invasiveness, and patient prognosis. Tumour Biol 36:2309–2321

Stubbs M, McSheehy PM, Griffiths JR, Bashford CL (2000) Causes and consequences of tumour acidity and implications for treatment. Mol Med Today 6:15–19

Suh DH, Kim MA, Kim H, Kim MK, Kim HS et al (2014) Association of overexpression of hexokinase II with chemoresistance in epithelial ovarian cancer. Clin Exp Med 14:345–353

Sung JY, Kim GY, Lim SJ, Park YK, Kim YW (2010) Expression of the GLUT1 glucose transporter and p53 in carcinomas of the pancreatobiliary tract. Pathol Res Pract 206:24–29

Swartz JE, Pothen AJ, van Kempen PM, Stegeman I, Formsma FK et al (2016) Poor prognosis in human papillomavirus-positive oropharyngeal squamous cell carcinomas that overexpress hypoxia inducible factor-1alpha. Head Neck 38:1338–1346

Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H et al (2007) Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 25:4414–4422

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8:16

Wang J, Yuan W, Chen Z, Wu S, Chen J et al (2012) Overexpression of G6PD is associated with poor clinical outcome in gastric cancer. Tumour Biol 33:95–101

Wang X, Li X, Zhang X, Fan R, Gu H et al (2015a) Glucose-6-phosphate dehydrogenase expression is correlated with poor clinical prognosis in esophageal squamous cell carcinoma. Eur J Surg Oncol 41:1293–1299

Wang Y, Zhang X, Zhang Y, Zhu Y, Yuan C et al (2015b) Overexpression of pyruvate kinase M2 associates with aggressive clinicopathological features and unfavorable prognosis in oral squamous cell carcinoma. Cancer Biol Ther 16:839–845

Warburg O (1956a) On the origin of cancer cells. Science 123:309–314

Warburg O (1956b) On respiratory impairment in cancer cells. Science 124:269–270

Warburg O, Wind F, Negelein E (1927) The metabolism of tumors in the body. J Gen Physiol 8:519–530

Williamson PR, Smith CT, Hutton JL, Marson AG (2002) Aggregate data meta-analysis with time-to-event outcomes. Stat Med 21:3337–3351

Yan S, Coffing BN, Li Z, Xie H, Brennick JB et al (2016) Diagnostic and prognostic value of ProEx C and GLUT1 in melanocytic lesions. Anticancer Res 36:2871–2880

Yang Z, Wu Z, Liu T, Han L, Wang C et al (2014) Upregulation of PDK1 associates with poor prognosis in esophageal squamous cell carcinoma with facilitating tumorigenicity in vitro. Med Oncol 31:337

Yu ZT, Zhao HF, Shang XB (2008) Expression of hypoxia-inducible factor-1alpha and vessel endothelial growth factor in esophageal squamous cell carcinoma and clinico-pathological significance thereof. Zhonghua Yi Xue Za Zhi 88:2465–2469

Yu G, Yu W, Jin G, Xu D, Chen Y et al (2015a) PKM2 regulates neural invasion of and predicts poor prognosis for human hilar cholangiocarcinoma. Mol Cancer 14:193

Yu M, Zhou Q, Zhou Y, Fu Z, Tan L et al (2015b) Metabolic phenotypes in pancreatic cancer. PLoS One 10:e0115153

Yuan C, Li Z, Wang Y, Qi B, Zhang W et al (2014) Overexpression of metabolic markers PKM2 and LDH5 correlates with aggressive clinicopathological features and adverse patient prognosis in tongue cancer. Histopathology 65:595–605

Zhan C, Shi Y, Lu C, Wang Q (2013) Pyruvate kinase M2 is highly correlated with the differentiation and the prognosis of esophageal squamous cell cancer. Dis Esophagus 26:746–753

Zhang D, Wang Y, Dong L, Huang Y, Yuan J et al (2013a) Therapeutic role of EF24 targeting glucose transporter 1-mediated metabolism and metastasis in ovarian cancer cells. Cancer Sci 104:1690–1696

Zhang X, He C, He C, Chen B, Liu Y et al (2013b) Nuclear PKM2 expression predicts poor prognosis in patients with esophageal squamous cell carcinoma. Pathol Res Pract 209:510–515

Zhang MX, Hua YJ, Wang HY, Zhou L, Mai HQ et al (2016a) Long-term prognostic implications and therapeutic target role of hexokinase II in patients with nasopharyngeal carcinoma. Oncotarget 7:21287–21297

Zhang ZF, Feng XS, Chen H, Duan ZJ, Wang LX et al (2016b) Prognostic significance of synergistic hexokinase-2 and beta2-adrenergic receptor expression in human hepatocelluar carcinoma after curative resection. BMC Gastroenterol 16:57

Zhao Y, Liu H, Riker AI, Fodstad O, Ledoux SP et al (2011) Emerging metabolic targets in cancer therapy. Front Biosci (Landmark Ed) 16:1844–1860

Zhao Y, Shen L, Chen X, Qian Y, Zhou Q et al (2015) High expression of PKM2 as a poor prognosis indicator is associated with radiation resistance in cervical cancer. Histol Histopathol 30:1313–1320

Zhou S, Wang S, Wu Q, Fan J, Wang Q (2008) Expression of glucose transporter-1 and - 3 in the head and neck carcinoma—the correlation of the expression with the biological behaviors. ORL J Otorhinolaryngol Relat Spec 70:189–194

Zhuang L, Scolyer RA, Murali R, McCarthy SW, Zhang XD et al (2010) Lactate dehydrogenase 5 expression in melanoma increases with disease progression and is associated with expression of Bcl-XL and Mcl-1, but not Bcl-2 proteins. Mod Pathol 23:45–53