T.C.
DOKUZ EYLÜL UNIVERSITY
IZMIR INTERNATIONAL
BIOMEDICINE AND GENOME
INSTITUTE

APPLICATION OF COMPUTATIONAL METHODS FOR INVESTIGATING THE ROLE OF VIMENTIN IN CANCER PROGNOSIS AND DIAGNOSIS

HALİL İBRAHİM PAZARBAŞI

MOLECULAR BIOLOGY AND GENETICS

DOCTORAL THESIS

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THESIS CODE: DEU.HSI.PhD-2017850015

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Dokuz Eylül University İzmir International Biomedicine and Genome Institute, Department of Genomics and Molecular Biotechnology, Molecular Biology and Genetics graduate program doctoral student Halil İbrahim PAZARBAŞI has successfully completed his doctoral thesis titled **'APPLICATION OF COMPUTATIONAL METHODS FOR INVESTIGATING THE ROLE OF VIMENTIN IN CANCER PROGNOSIS AND DIAGNOSIS'** on the date of 02/09/2024.

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LIST OF ABBREVIATIONS

AC-MPC	Adenocarcinoma with Micropapillary Component
AQUA	Automated Quantitative Immunohistochemistry
BLBC	Basal-Like Breast Cancer
CAF	Cancer-Associated Fibroblast
ccRCC	Clear-Cell Renal Cell Carcinoma
CIs	Confidence Intervals
CRC	Colorectal Cancer
DFS	Disease-Free Survival
DSS	Disease Specific Survival
EC	Endometrial Carcinoma
EMT	Epithelial-Mesenchymal Transition
EOC	Epithelial Ovarian Cancer
ESCC	Esophageal Squamous Cell Carcinoma
GBAC	Gallbladder Adenocarcinoma
GBM	Glioblastoma Multiforme
GC	Gastric Cancer
HB	Hepatoblastoma
HCC	Hepatocellular Carcinoma
HNSCC	Head And Neck Squamous Cell Carcinoma
HR	Hazard Ratio
IDC (NOS)	Invasive Ductal (Not Otherwise Specified Carcinoma)
IHC	Immunohistochemistry
IHCC or ICC	Intrahepatic Cholangiocarcinoma
LMS	Leiomyosarcoma
LSCC	Laryngeal Squamous Cell Carcinoma
MFS	Metastasis-Free Survival
NMIBC	Non-Muscle İnvasive Bladder Cancer
NPC	Nasopharyngeal Cancer/Carcinoma
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival

OSCC	Oral Squamous Cell Carcinoma
OTSCC	Oral Tongue Squamous Cell Carcinoma
PC	Prostate Cancer
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
RCC	Renal Cell Carcinoma
RFS	Recurrence-Free Survival
SCC	Squamous Cell Carcinoma
SIAC	Small Intestinal Adenocarcinoma
SqCC	Squamous Cell Carcinoma
SqCLC	Squamous Cell Lung Cancer
TNBC	Triple-Negative Breast Cancer
TSCC	Thymic Squamous Cell Carcinoma
VIFs	Vimentin Intermediate Filaments
VIM	Vimentin

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Halil İbrahim PAZARBAŞI

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Application of computational methods for investigating the role of vimentın in cancer prognosis and diagnosis

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ABSTRACT

Vimentin, a cytoskeletal protein implicated in various cellular processes, has garnered significant interest as a potential prognostic biomarker in cancer. Herein, a systematic literature review and meta-analysis was conducted in order to investigate the prognostic significance of vimentin expression across diverse cancer types through *in silico* approaches. A comprehensive search yielded 115 eligible studies encompassing 14,784 patients, representing a broad spectrum of cancers. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to assess the association between vimentin expression and patients' survival outcomes, including overall survival (OS), recurrence-free/disease-free survival (RFS/DFS), progression-free/metastasis-free survival (PFS/MFS) and disease-specific survival (DSS). Our analysis revealed a significant correlation between elevated vimentin expression and adverse survival outcomes across multiple cancer types. Specifically, increased vimentin expression was associated with poorer OS, RFS/DFS, PFS/MFS and DSS. These findings were robust and consistent across diverse cancer cohorts. Furthermore, when the studies were classified based on the host country's income, a significant association was found between vimentin overexpression and poorer OS in the lower-middle income subgroup. Collectively, our meta-analysis provides compelling evidence supporting vimentin as a promising prognostic biomarker across a wide range of human cancers. These findings underscore the potential clinical utility of vimentin in prognostic stratification and personalized decision-making for cancer patients.

Key Words: Vimentin, Cancer, Prognosis, Meta-analysis, Biomarker, Survival Analysis

Vimentinin kanser prognozu ve teşhisinde rolünü araştırmak için hesaplamalı yöntemlerin uygulanması

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ÖZET

Çeşitli hücresel süreçlerde rol oynayan bir iskelet proteini olan vimentin, kanserde potansiyel bir prognostik biyomarker olarak ilgi çekmiştir. Bu çalışmada, çeşitli kanser türlerinde vimentin ekspresyonunun prognostik önemini araştırmak amacıyla sistematik bir literatür taraması ve meta-analiz çalışması yapılmıştır. Yapılan kapsamlı arama sonucunda, çeşitli kanser türlerinden 14.784 hastayı kapsayan 115 uygun çalışma tespit edilmiştir. Vimentin ekspresyonu ile hastaların sağkalım sonuçları (genel sağkalım (OS), nükssüz/hastalıksız sağkalım (RFS/DFS), ilerlemesiz/metastazsız sağkalım (PFS/MFS) ve hastalığa özgü sağkalım (DSS)) arasındaki ilişkiyi değerlendirmek için %95 güven aralıkları (CIs) ile birleşik risk oranları (HRs) hesaplanmıştır. Analizimiz, artan vimentin ekspresyonu ile birçok kanser türünde olumsuz sağkalım sonuçları arasında anlamlı bir korelasyon ortaya koymuştur. Özellikle, artan vimentin ekspresyonu olumsuz OS, RFS/DFS, PFS/MFS ve DSS ile ilişkilendirilmiştir. Bu bulgular, çeşitli kanser kohortları arasında tutarlı sonuçlar vermiştir. Ayrıca dahil edilen çalışmalar, çalışmanın yapıldığı ülkenin gelirine göre sınıflandırıldığında, düşük-orta gelir grubunda vimentinin aşırı ekspresyonu ile daha kötü genel sağkalım arasında anlamlı bir ilişki bulunmuştur. Yapılan meta-analiz çalışmasında, vimentinin geniş bir insan kanseri yelpazesinde umut verici bir prognostik biyomarker olduğunu destekleyen güçlü kanıtlar yer almaktadır. Bu bulgular, vimentinin prognostik sınıflandırmada ve kanser hastaları için kişiselleştirilmiş karar vermede potansiyel klinik faydasını vurgulamaktadır.

Anahtar Sözcükler: Vimentin, Kanser, Prognoz, Meta-Analiz, Biyomarker, Sağkalım Analizi

1. INTRODUCTION AND OBJECTIVES

1.1. Description and Significance of the Issue

Meta-analysis is a systematic review of a focused topic in the literature that provides a quantitative estimate for the effect of a treatment intervention or exposure. The key to designing a high quality meta-analysis is to identify an area where the effect of the treatment or exposure is uncertain and where a relatively homogenous body of literature exists. The techniques used in meta-analysis provide a structured and standardized approach for analyzing prior findings in a specific topic in the literature. Meta-analysis findings may not only be quantitative but also may be qualitative and reveal the biases, strengths, and weaknesses of existing studies. The results of a meta-analysis can be used to form treatment recommendations or to provide guidance in the design of future clinical trials (Russo, 2007).

Identifying robust biomarkers for precise and timely diagnosis, prognosis, and evidence-based decision-making across various cancer types remains a significant challenge in clinical and medical research (Das et al., 2023; Fountzilas et al., 2023; Liu et al., 2014; Yu et al., 2019; Zhang et al., 2020). With the continuous influx of quantitative and qualitative data from clinical trials and studies, meta-analysis has become a crucial tool in clinical practice and public health. This statistical approach combines the quantitative results from multiple scientific studies addressing the same question, enhancing in this way statistical power and resolving conflicts among individual studies (Forero et al., 2019; Papakostidis & Giannoudis, 2023; Shadish & Lecy, 2015).

Vimentin is a crucial component of the interstitial cell skeleton. The expression levels of vimentin are increased during epithelial-to-mesenchymal transition (EMT) and closely correlated with cancer invasion and metastasis. Moreover, Vimentin plays a role in cell cycle regulation and adhesion, highlighting its significance in cancer development and progression (Lin et al., 2017). Nonetheless, despite the well-documented role of vimentin in cancer biology and progression, a comprehensive meta-analysis of the predictive value of vimentin expression in cancer is lacking. Although several meta-analysis studies have been conducted on the association of vimentin with cancer clinical outcomes, these studies include a limited number of

studies and therefore encompass a low number of patients. In addition, the meta-analysis studies conducted to date have examined the relationship between vimentin and survival in a group of patients with a single type of cancer.

The present study provides an updated and comprehensive meta-analysis on the prognostic significance of vimentin in various human cancers. By implementing strict inclusion and exclusion criteria, we included 115 eligible studies, a sufficiently large number for a robust meta-analysis.

1.2. Hypothesis of the Study

A comprehensive meta-analytic study that includes all possible cancer types and statistically significant results to associate elevated vimentin expression with poor clinical outcomes, including reduced survival rates and increased likelihood of metastasis in a large patient group, could further support the role of vimentin as a prognostic biomarker.

1.3. Aims of the Study

The aim of this study is to investigate the role of vimentin as a potential prognostic biomarker for overall survival, cancer recurrence, cancer progression, and metastasis across various cancer types by conducting systematic literature review and meta-analysis.

2. GENERAL INFORMATION

2.1. Application of meta-analysis for determining cancer biomarkers

Herein, we present a methodological guide for conducting meta-analyses using transparent and reproducible methods to derive valid conclusions from the existing body of research.

2.1.1. Defining the research question

The first step in conducting a meta-analysis is to formulate a clear and well-defined research question (Shaheen et al., 2023). For instance, one might ask whether HOTAIR expression is linked to survival rates in human cancers. Researchers should provide a background on the topic, referencing current knowledge, and clearly state the primary objectives of the meta-analysis. In a study the authors highlighted gaps in the scientific literature and outlined their research goals, which included performing a comprehensive and updated meta-analysis to assess the prognostic significance of HOTAIR expression in cancer (Toy et al., 2019). Their analysis revealed a significant positive correlation between HOTAIR overexpression and poor overall survival, as well as progression/metastasis-free and recurrence/disease-free survival, across various types and subtypes of human cancers (Toy et al., 2019).

2.1.2. Systematic Literature Review

Conducting a systematic review to collect both published and unpublished studies is a challenging aspect of meta-analysis. To maximize the retrieval of relevant studies, it is recommended to search multiple bibliographic databases, such as MEDLINE/PubMed, Scopus, Embase, The Cochrane Central Register of Controlled Trials, Web of Science, and Google Scholar (Falagas et al., 2008). An extensive, often manual, search of these scientific databases is carried out using a combination of relevant search terms. Initially, the titles and abstracts of the articles are scanned to exclude irrelevant studies. The reference lists of review articles can also be examined

to identify additional articles that may have been missed in the initial search. The selected articles are then filtered based on established inclusion criteria (e.g., publication in English, minimum sample size) and exclusion criteria (e.g., not original research, inadequate sample size). The key variables to be extracted from the eligible studies should be defined. Broad inclusion criteria may increase heterogeneity among studies, while narrow inclusion criteria may limit the number of relevant studies (Forero et al., 2019; Nikolopoulos et al., 2011).

2.1.2.1. Quality Assessment of Included Studies

Evaluating the quality of the included studies can help researchers refine their inclusion/exclusion criteria and assess the representativeness of the study samples. Various tools are commonly employed for this purpose: the Jadad scale (Jadad et al., 1996) for randomized clinical trials, the Newcastle-Ottawa scale (Moskalewicz & Oremus, 2020; Stang, 2010) for non-randomized studies, AXIS (Downes et al., 2016) for cross-sectional studies, and QUADAS-2 (Whiting et al., 2011) for diagnostic accuracy studies.

2.1.2.2. Data Extraction

Key data from the selected studies are extracted and recorded in a structured format, often using an Excel spreadsheet. If essential data are missing from the main text or supplementary materials, the corresponding authors were contacted to obtain the missing information. Moreover, it is recommended that these tasks be performed independently by two investigators, with any discrepancies resolved through consensus (Forero et al., 2019; Greco et al., 2013; Nikolopoulos et al., 2011).

2.1.2.3. Reporting Guidelines

Ensuring transparency, reliability, comprehensiveness, and replicability in a systematic review is aided by updated reporting guidelines established by international

consortia. Some examples include QUORUM (Quality of Reporting of Meta-analyses) (Clarke, 2000), MOOSE (Meta-analysis Of Observational Studies in Epidemiology) (Brooke et al., 2021), and the widely used PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Page et al., 2021). Additionally, specific guidelines have been developed for certain types of studies, such as CONSORT for randomized clinical trials (Hopewel et al., 2008) and STROBE guidelines for observational clinical studies (usually in the surgical discipline) (von Elm et al., 2007) , meta-analysis techniques specifically tailored for genetic association studies (Sagoo et al., 2009) and genome-wide association studies (GWAS) have also been developed to accommodate the unique complexities and large datasets associated with these fields(Evangelou & Ioannidis, 2013). These methods are essential for synthesizing data across multiple studies, allowing for more robust and reliable identification of genetic variants linked to diseases or traits.

2.1.3. Statistical Analyses

Once data had been collected, statistical analyses were performed using state-of-the-art, freely accessible software such as R (https://www.r-project.org/) or Stata (https://www.stata.com/) or standalone applications.

2.1.4. Effect Estimation

The choice of effect measure depends on the type of data, such as dichotomous, continuous, or time-to-event data. In epidemiological studies with binary outcomes, the overall effect can be measured using odds ratios (OR), relative risk (RR), or risk difference (RD). The OR (Ranganathan et al., 2015; Szumilas, 2010), for example, quantifies the association between exposure and outcome, and an OR greater than 1 suggests that the outcome is more likely to occur in the presence of the exposure. For instance, Zhu *et al.* (Zhu et al., 2017) used OR to demonstrate a significant correlation between PVT1 expression and lymph node metastasis, distant metastases, advanced tumor-node-metastasis (TNM) stage, and tumor size. Similarly, Wang and coworkers (Wang et al., 2021) found that heat shock protein 70 (HSP70) expression was strongly associated with higher tumor differentiation, intestinal gastric cancer, and lymphovascular invasion.

RR or risk ratio (Ranganathan et al., 2015; Sistrom & Garvan, 2004) measures the ratio of the risk of an event occurring in the exposed group compared to the unexposed group. Nassour *et al.* (Nassour et al., 2023) reported a higher RR of bladder and kidney cancer in Lynch syndrome patients. Risk difference (RD) (Kim, 2017) represents the difference in risk between the exposed and unexposed groups. For example, Nakamura *et al.* (Nakamura et al., 2024) found that heat-shock protein HSP40 is associated with a lower probability of lymph node dissemination, while HSF1 is linked to a higher probability.

Hazard ratio (HR) (Roberts et al., 2019) is typically used for time-to-event data, such as survival studies. HR compares the hazard rate of an event in an exposed group with that in an unexposed group. In the absence of reported HRs, they can be estimated from Kaplan-Meier curves using the Cox proportional hazards model (Tibshirani, 1982). For instance, Toy and colleagues (Toy et al., 2019) estimated HRs in cancer patients with high *HOTAIR* expression, finding a lower overall survival rate compared to those with low expression. Fang and collaborators (Fang et al., 2020) reported a significant positive correlation between elevated lncSNHG15 expression and poor overall and disease-free survival. Recently, de Moraes and colleagues (de Moraes et al., 2024) showed that breast cancer patients treated only with CDK inhibitors had a higher progression-free survival rate compared to those treated with both CDK inhibitors and PPIs.

2.1.5. Forest Plot

The results of meta-analyses are typically displayed using forest plots (Lewis & Clarke, 2001) (**Figure 1**), which graphically represent the estimated effect sizes for each study along with their 95% confidence intervals, as well as the pooled effect, which is the weighted average of the individual estimates.

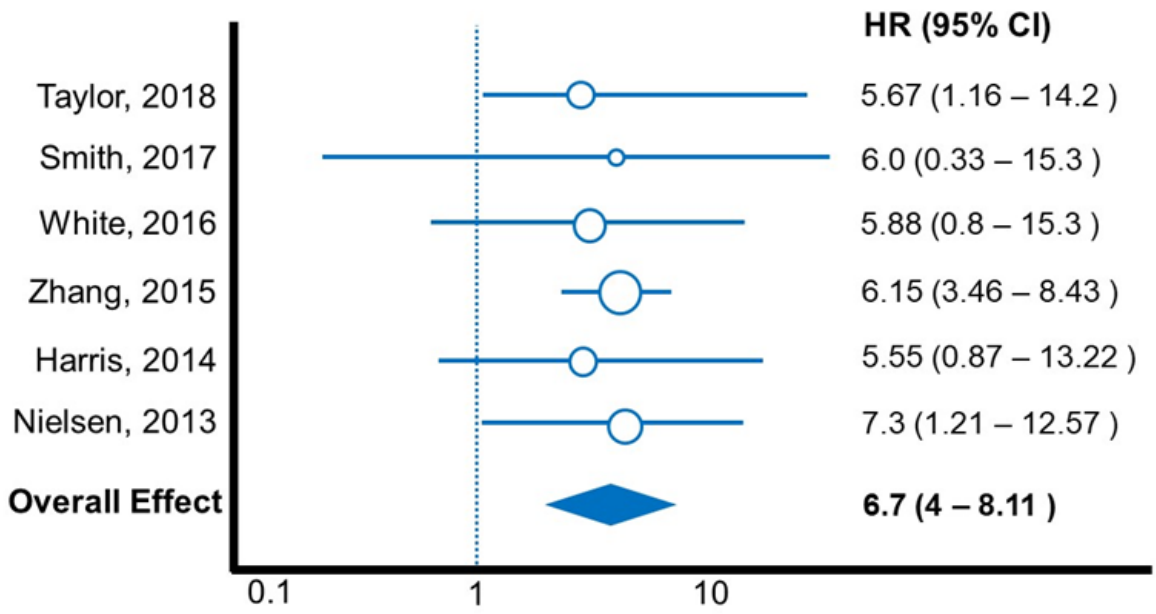


Figure 1. Example forest plot of hazard ratios. The left column lists individual studies in chronological order, identified by the first author's name and publication year. Each study's effect measure is depicted as a circle, with whiskers representing the 95% confidence interval (CI). The size of the circle corresponds to the study's weight in the meta-analysis, with larger studies contributing more weight. The overall effect is indicated by a diamond, and the width of the diamond illustrates the 95% CI of the pooled estimate.

2.1.6. Selection of The Best Fit Statistical Model

Most meta-analyses use either a fixed-effect or random-effects model (Dettori et al., 2022) to calculate the overall effect. The fixed-effects model assumes a single common true effect size among studies, while the random-effects model assumes that true effects vary across studies and calculates the overall effect as the weighted average of the individual effects.

2.1.7. Heterogeneity

Studies included in a meta-analysis often differ in design, methodology, data processing, and analysis, leading to heterogeneity, which represents the degree of variation among studies. Assessing and quantifying heterogeneity is crucial to determine whether it is appropriate to combine the studies in the meta-analysis. Several metrics are used for this purpose (Cordero & Dans, 2021; Sedgwick, 2015a).

Cochran's Q test (Cochran, 1950) is a non-parametric statistical test that examines whether all studies have the same effect size. A p-value less than 0.05 indicates the presence of heterogeneity. Another solid metric, the Higgins I^2 statistic (Higgins et al., 2003) estimates the percentage of observed variation across studies attributable to real heterogeneity rather than chance. I^2 is calculated with the formula $(Q-df)/Q\times100\%$, where 'Q' is the Cochran test and 'df' is the degrees of freedom. I^2 values range from 0% (no heterogeneity) to 100% (high heterogeneity). Typically, if $I^2 \geq 50\%$, a random-effects model is applied; otherwise, a fixed-effects model is used (Toy et al., 2019).

Subgroup analysis (Richardson et al., 2019) is often employed to explore heterogeneity further. Studies are grouped based on specific characteristics (e.g. the ethnicity, the types of cancer by primary anatomical site, the endocrine gland neoplasms, the types of squamous cell carcinoma, the data extraction method, the income of the country where healthcare is provided), and separate meta-analyses are conducted for each subgroup to detect any statistically significant differences.

2.1.8. Sensitivity Analysis

Sensitivity analysis is performed to assess the robustness of the results (**Figure 2**). This involves sequentially omitting one study, repeating the meta-analysis, and evaluating the impact of the omitted study on the overall effect size. If a study significantly affects the overall effect size, it may contribute to between-study variation.

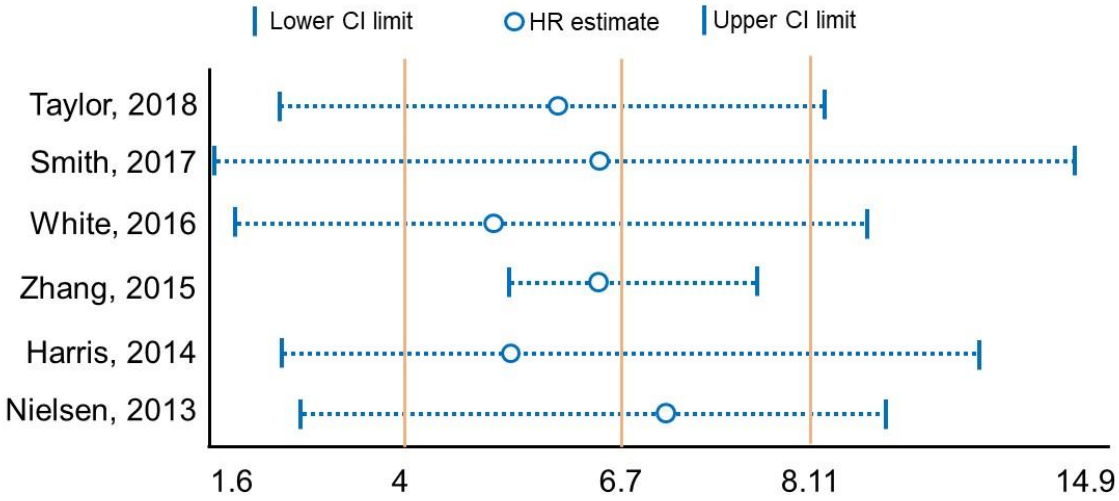


Figure 2. Example sensitivity analysis. The results remain consistent with the inclusion or exclusion of any individual study. The pooled hazard ratio (HR) and 95% confidence interval (CI) are unchanged, indicating that no single study significantly influences the overall findings.

2.1.9. Publication Bias

Publication bias (Sedgwick, 2015b) is a significant concern in meta-analyses, as studies with statistically insignificant results are less likely to be published than those with significant findings. Assessing and addressing publication bias is essential for ensuring the validity and reliability of the meta-analysis (Lin & Chu, 2018; Shaheen et al., 2023). Several methods are available to detect publication bias (Jin et al., 2015).

A quasi-statistical method, the funnel plot (Egger et al., 1997), allows for the visual inspection of potential publication bias. This scatterplot displays the standard errors of the effect estimates from individual studies on the horizontal axis against the standard error of the estimated effect on the vertical axis. An inverted funnel plot that appears symmetrical suggests the absence of publication bias, whereas an asymmetrical plot indicates its presence (**Figure 3**). In such plots, smaller studies often exhibit a wider scatter at the bottom, reflecting less precision, while larger studies show a narrower spread, being closer to the true effect size due to their greater precision.

The Begg and Mazumdar adjusted rank correlation test is a statistical analogue of the funnel plot, used to identify significant correlations between effect estimates and their variances (Begg & Mazumdar, 1994). The Egger's test (Egger et al., 1997), another method, performs a linear regression of standardized effect estimates on their

standard errors, with a p-value less than 0.05 indicating statistically significant publication bias.

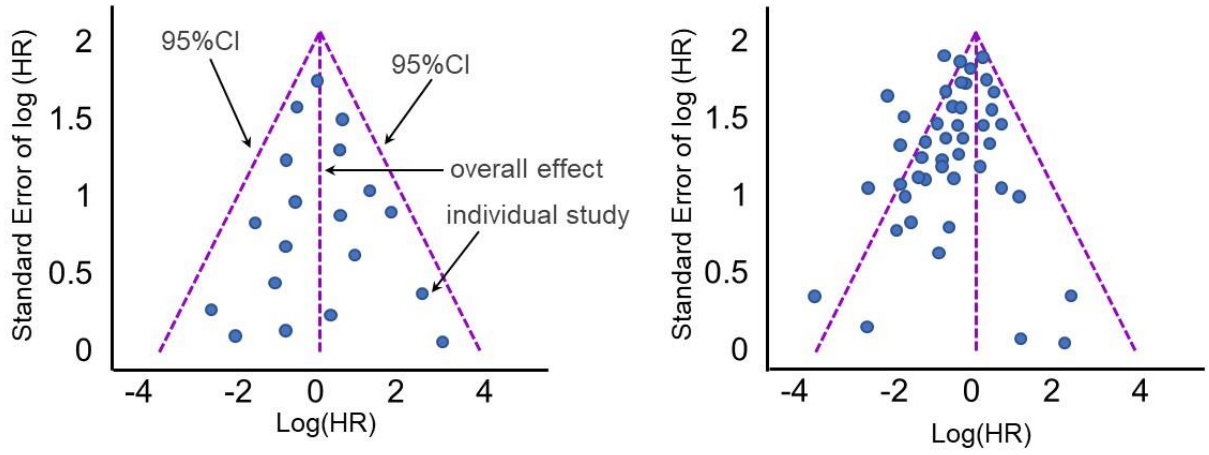


Figure 3. Example of funnel plots. The graphic on the left represents the symmetrical funnel plot, and the right represents the asymmetrical funnel plot.

2.2. Meta-analysis of the prognostic significance of Vimentin in cancer

2.2.1. Vimentin molecule

Vimentin, a type III cytoplasmic intermediate filament (IF) protein assembling into extensive cytoskeletal networks, plays a crucial role in maintaining cell structure and integrity. This 57-kD protein is highly conserved and ubiquitously present. Vimentin is consistently expressed in mesenchymal cells, including endothelial cells lining blood vessels, renal tubular cells, leukocytes, fibroblasts, neutrophils, and macrophages (Crystal et al., 2008; Fuchs & Weber, 1994; McKeon et al., 1986; Satelli & Li, 2011; Steinert, 1993; Steinert et al., 1993). The vimentin polypeptide consists of 466 amino acids, featuring a highly conserved α-helical "rod" domain flanked by non-α-helical N- and C-terminal domains, referred to as the "head" (77 residues) and "tail" (61 residues), respectively (Goldie et al., 2007). Vimentin IFs (VIFs) play roles in various cellular functions, including the development of focal adhesions (Tsuruta & Jones, 2003), stress-fiber assembly (Jiu et al., 2017), invadopodia elongation (Schoumacher et al., 2010), and the regulation of microtubule dynamics (Gan et al., 2016; Shabbir et al., 2014), as well as in viral infections (Suprewicz et al., 2021; Yu et al., 2016). The assembly of VIFs and vimentin expression are well-established markers and regulators of the EMT (Mendez et al., 2010). They play a critical role in various stages of cancer

initiation and progression (Kidd et al., 2014; Satelli & Li, 2011), as well as in other pathological conditions (Danielsson et al., 2018; Eibauer et al., n.d.; Henderson et al., 2012).

Vimentin is encoded by a single-copy gene located on chromosome 10p13. Early research studies identified three distinct elements within the vimentin promoter that regulate its expression (Rittling & Baserga, 1987). Subsequent studies have revealed several *cis*-elements and associated factors within the human vimentin promoter, indicating that the gene is under complex regulatory control (Satelli & Li, 2011). These include a TATA box, eight putative GC-boxes (Rittling & Baserga, 1987), NF-κB binding site (Lilienbaum & Paulin, 1993), AP-1 binding site (Rittling et al., 1989), PEA3 binding site (Chen et al., 1996), Sp/XKLF binding site (Zhang et al., 2003), and ZBP-89 binding site (Wieczorek et al., 2000). Additionally, vimentin expression has been shown to be transactivated by β-catenin/TCF, which binds to a site 468 bp upstream of the transcription initiation site in the vimentin promoter, thereby enhancing the invasive potential of tumor cells (Gilles et al., 2003).

2.2.1. Vimentin in EMT

Epithelial to mesenchymal transition (EMT) is a reversible biological process where epithelial cells undergo a transformation, losing their distinct characteristics such as apicobasal polarity, intercellular junctions, epithelial markers, and stable cytoskeletal organization. This transition leads them to acquire a mesenchymal phenotype, which is characterized by enhanced mobility, invasiveness, and a loss of differentiation (Kalluri & Weinberg, 2009). Importantly, the role of EMT in cancer extends beyond epithelial-origin cancers to include non-epithelial cancers such as glioma and hematological malignancies (Kahlert et al., 2017).

EMT can be classified into three types depending on the tissue context and pathophysiological conditions: Type-1 EMT occurs during organogenesis and embryonic development, such as in gastrulation or the migration of cells from the neural crest. Type-2 EMT is involved in wound healing, promoting cell migration, growth, and organ fibrosis (Roche, 2018). Type-3 EMT is associated with the onset and progression of various diseases, including cancer and metastasis (Usman et al., 2021).

At the molecular level, vimentin over-expression is linked to EMT, a significant alteration in the adhesion and migration properties of cancer cells (Hugo et al., 2007). Vimentin, a mesenchymal-specific protein, is generally not expressed in normal epithelial cells but is induced when cells undergo epithelial-mesenchymal transition (EMT). Thus, elevated vimentin expression can be considered a hallmark of EMT (Liu et al., 2016).

EMT is a complex process that involves the coordinated interaction of various networks, including inducers, core regulators, and effectors. Key inducers of EMT include transforming growth factor-beta (TGF-β), bone morphogenetic protein (BMP), receptor tyrosine kinase (RTK), Wnt/β-catenin, NOTCH, hedgehog, signal transducer and activator of transcription 3 (STAT3), extracellular matrix (ECM)-mediated pathways, and hypoxia signaling (Gonzalez & Medici, 2014; Yeo et al., 2017). These inducers trigger the expression and activation of EMT core regulators, notably three major groups of EMT-activating transcription factors (EMT-TFs): the Snail family (Snail/Slug), the ZEB family (ZEB1/ZEB2), and the Twist family (TWIST1/TWIST2) (Georgakopoulos-Soares et al., 2020). Additional EMT-TFs include c-Myc, FOXC2, and HIF1. The activation of these EMT-TFs is further refined by epigenetic modifications, which lead to the expression of various EMT effectors that determine the cell's identity (Lin & Wu, 2020; Usman et al., 2021).

During EMT, the expression of epithelial proteins are downregulated by the cells, including those that are part of cell junction complexes (Huang et al., 2012). Epithelial biomarkers, including E-cadherin, EpCAM, claudins, occludins, and cytokeratins, experience a decrease in expression, while mesenchymal markers like vimentin, α-SMA, fibronectin, N-cadherin, and integrin β6 show an increase in expression (Scanlon et al., 2013).

Vimentin filaments provide cancer cells with a viscoelastic framework that shields them from mechanical stress during migration or when passing through tight spaces. These filaments also help maintain the positioning and integrity of organelles, particularly the nucleus, during EMT and the progression of cancer. Additionally, it has been reported that vimentin safeguards cancer cells from the internal stress caused by misfolded proteins by directly binding to stress granules and aggresomes, aiding in their subsequent breakdown (Pattabiraman et al., 2020; Patteson et al., 2019).

Cancer stem cells (CSCs) are a small subset of cells with the ability to self-renew and are known for their resistance to therapies and immune responses. These pluripotent cells can initiate new tumors at distant sites (Usman et al., 2020). It has been suggested that EMT can convert non-CSCs into cancer stem cells, which are consistently vimentin-positive (Carnero & Lleonart, 2016). CSCs are believed to arise from interactions and adaptations within the tumor microenvironment and through therapeutic interventions, leading to a diverse subpopulation. Hypoxia, or low oxygen conditions, plays a significant role in the development of CSC traits, including self-renewal, EMT, and drug resistance. Hypoxia-inducible factors (HIFs) are key mediators of cellular responses to hypoxia, such as proliferation, EMT, and metastasis. Other signaling pathways, including TGF-β, Wnt/β-catenin, TNF-α, and NF-κB, also regulate stemness through HIFs and contribute to EMT by controlling the expression of transcription factors like SNAI1, TWIST, ZEB1, SLUG, and TCF3, which in turn lead to vimentin expression (Usman et al., 2021).

3. MATERIALS AND METHODS

3.1. Type of the Study

This study was carried out using in silico methods and data from publicly accessible sources.

3.2. Time and the Location of the Study

This study was conducted at Izmir Biomedicine and Genome Institute in the period of time between December 2020 and March 2024.

3.3. Materials of the Study

All relevant research articles studied on the relationship between vimentin expression and cancer survival were sourced from the PubMed/MEDLINE biomedical literature database (Fiorini et al., 2017).

3.4. Research variables

The main variable in the study was the vimentin expression level (low versus high), which was investigated for the evaluation of OS, RFS/DFS, PFS/MFS and DSS in various cancer groups.

3.5. Programming Languages and Tools for Data Processing

- Engauge Digitizer (Tierney et al., 2007).
- STATA statistical software version 13.0 (Stata Corporation, College Station, TX, USA).
- Microsoft Excel.

3.6. Data Analysis

3.6.1. Searching Strategy and Study Eligibility Criteria

To ensure methodological rigor, we conducted a systematic review and meta-analysis in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page et al., 2021). A comprehensive search

for relevant scientific studies examining the correlations between vimentin expression and prognosis across various cancer types was performed on the PubMed/MEDLINE (Fiorini et al., 2017) bibliographic database. The search process involved a meticulous manual examination, utilizing a combination of pertinent keywords to retrieve relevant publications: (“vimentin” OR “VIM” OR “vmt”) AND (“cancer” OR “carcinoma” OR “tumor” OR “tumour” OR “neoplasm” OR “malignancy”) AND (“prognosis” OR “survival” OR “incidence” OR “outcome” OR “mortality” OR “death”).

For a study to be deemed eligible for inclusion in this study, it had to meet the following predetermined criteria: (1) studies of human clinical trials, (2) studies including more than 30 patients in total, (3) the correlation between vimentin expression and cancer patients’ survival was estimated, (4) availability of HR and 95% confidence interval (CI) or survival curves or sufficient data to calculate HR and 95% CI, (5) quantitative measurement (e.g., qPCR) of vimentin expression in cancers was included, (6) studies published in English, (7) studies with statistically significant survival data ($p<0,05$).

In contrast, studies were excluded from consideration based on the predetermined exclusion criteria: (1) Not original article (i.e., case reports, reviews, letters, editorials, meta-analysis, commentaries, and unpublished data); (2) Non-English articles; (3) Not a human study (e.g. laboratory studies on cell lines or animal models); (4) Irrelevant studies (i.e. not related to vimentin, survival or cancer prognosis) (5) Insufficient survival data (e.g. not divided into high and low vimentin groups); (6) studies including less than 30 patients in total; (7) Insufficient tissue samples or samples other than tissue (e.g., blood, serum); (8) studies with not statistically significant survival data ($p\geq0,05$).

3.6.2. Study Selection, Data Extraction, and Quality Assessment

The identification of potential studies was carried out independently by two authors (Halil İbrahim Pazarbaşı (H.I.P.) and Didem Ökmen (D.O.)) from the available literature. Quality assessment of these studies was conducted independently by H.I.P. and D.O., with any discrepancies resolved through consultation with a third investigator (Athanasia Pavlopoulou) (Mathew, 2022; Russo, 2007). Data relevant to the research were extracted from the included studies and systematically recorded in a customized

Excel worksheet. In instances where the Hazard Ratio (HR) was not explicitly reported in the respective articles, data were extracted from graphical survival plots (i.e., Kaplan-Meier curves) using Engauge Digitizer v10.11 software, following established procedures.

3.6.3. Statistical analysis

All statistical analyses were executed using STATA statistical software version 13.0 (Stata Corporation, College Station, TX, USA), and Microsoft Excel. To assess the heterogeneity among the included studies, the Higgins I-squared (I^2) statistic was employed, with categorization as follows: I^2 < 25% denoted no heterogeneity, 25%<I^2<50% indicated low heterogeneity, 50%<I^2<75% signified moderate heterogeneity, and I^2 > 75% represented high heterogeneity (Higgins et al., 2003; Higgins & Thompson, 2002). In instances of statistically significant heterogeneity (I2 > 50% and Ph < 0.05), a random-effects model was employed; otherwise, a fixed-effects model (DerSimonian & Laird, 1986, 2015) was used. Sensitivity analysis was conducted by systematically excluding individual studies to validate the consistency of outcomes. Potential publication bias was assessed through Begg's funnel plot (Begg & Mazumdar, 1994) and Egger's test (Egger et al., 1997), with a p-value less than 0.05 considered indicative of statistically significant publication bias.

4. RESULTS

4.1. Study Selection Process and Characteristics of Included Studies

A comprehensive search of the biomedical literature yielded a total of 54,980 relevant scientific studies published or accepted until December 31, 2020. Following the application of predefined inclusion and exclusion criteria, 115 studies were deemed eligible for inclusion in this meta-analysis, as illustrated in **Figure 4**. **Table 1** provides a summary of key characteristics extracted from these included studies, encompassing details such as the surname of the first author, year of publication, country of origin, cancer type, duration of follow-up (in months), total patient count, vimentin expression detection method, hazard ratios (HR) with corresponding 95% confidence intervals (CI) for various survival endpoints including overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS), and metastasis-free survival (MFS), as well as data extraction methodology and specimen type. In total, the meta-analysis comprised 14,784 patients across 115 cohorts spanning the years 1990 to 2022, with reported follow-up periods ranging from 24 to 302 months. The measurement of vimentin expression levels encompassed techniques such as quantitative reverse transcription polymerase chain reaction (qRT-PCR), microarrays, and immunohistochemistry (IHC) staining methods. The HRs that were not included in the subsequent steps of the analysis because they were not considered statistical significant (i.e., p-value > 0.05) are shown in red.

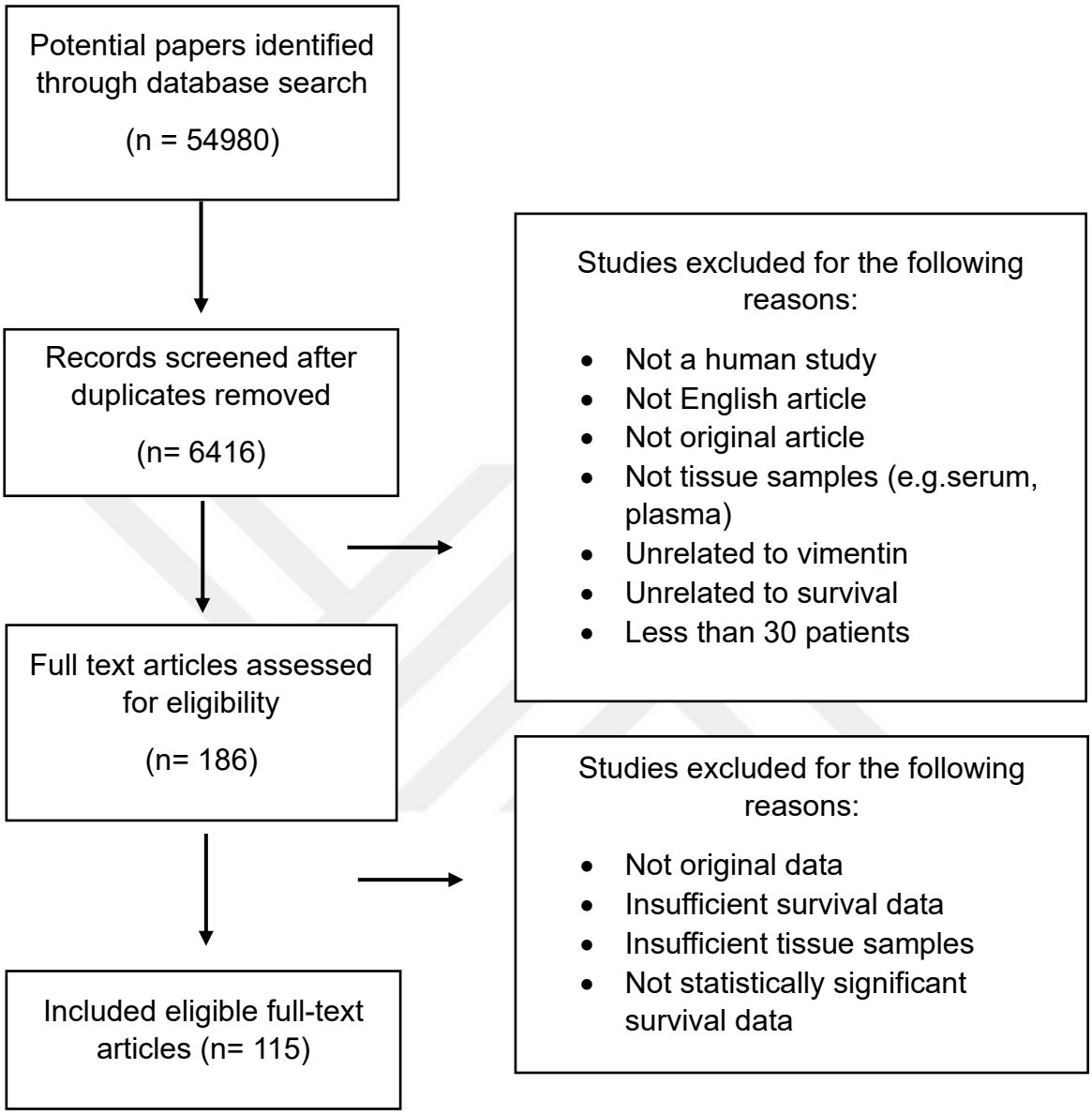


Figure 4. Flowchart used in study selection.

Table 1. Characteristics of the studies included in the meta-analysis

Author (Year)	Country	Cancer Type	Maximum months of follow up	High Expression	Low Expression	Total Cases	HR of OS	p-value	DFS/ RFS	p-value	HR of MFS/ PFS	p-value	HR of DSS	p-value	Assay method	Data extraction method
(Domagala et al., 1990)	Poland	Breast Cancer	60	22	61	83	2.381 (0.989–3.721)	0.0465							IHC	K-M
(Ueyama et al., 1993)	Japan	Gastric Cancer	100	5	133	138	1.203 (0.929–1.321)	0.0465							IHC	K-M
(Dehghani et al., 1998)	Germany	Oligodendroglioma	132	25	57	82	1.378 (1.185–2.525)	0							IHC	K-M
(Sabo et al., 1997)	Israel	RCC	180	17	22	39	2.003 (1.254–3.199)	0.001			1.47 (1.004–2.726)	0.004			IHC	K-M
(Moch et al., 1999)	Switzerland	RCC	241	139	144	283	1.177 (0.693–1.785)	0.017							IHC	K-M
(H. L. Kim et al., 2004)	USA	RCC	>120	NM	NM	44							2.48 (1.12-5.50)	0.026	IHC	Reported
(Rodríguez-Pinilla et al., 2007)	Spain	Breast Cancer	200	26	73	99							1.063 (0.6-1.69)	0.027	IHC	K-M
(Lien et al., 2007)	Taiwan	Breast Cancer	>100	10	134	144	2.383 (1.173–3.152)	0.001							IHC	K-M
(Ngan et al., 2007)	Japan	CRC	120	59	83	142	0.411 (0.188–0.901)	0.026	0.507 (0.25–1.025)	0.059					IHC	K-M
(Al-Saad et al., 2008)	Norway	NSCLC	179	302	33	335							2.695 (1.441-5.039)	0.002	IHC	Reported
(L.-K. Liu et al., 2010)	China	OSCC	170	20	37	57	1.142 (0.893–2.2169)	0.039							IHC	K-M
(M. A. Kim et al., 2009)	South Korea	Gastric Cancer	108	37	534	571	1.226 (0.804–1.476)	0.0288							IHC	K-M
(Fuyuhiro et al., 2010)	Japan	Gastric Cancer	177	86	179	265	1.481 (0. 893–3.113)	0.048							IHC	K-M
(Tseng et al., 2011)	Taiwan	OSCC	>60	32	33	65	0.45 (0.20–1.00)	0.05							IHC	Reported
(Handra-Luca et al., 2011)	USA	PDAC	101,95	94	60	154	1.53 (1.14–2.05)	0.01							IHC	Reported
(Otsuki et al., 2011)	Japan	Gastric Cancer	72	NM	NM	106			2.1 (1.0–4.4)	0.036			2.1 (1.0-4.5)	0.041	RT-PCR	Reported
(Albert et al., 2012)	France	TSCC	>70	14	30	44	4.48 (1.6–12.3)	0.0086							IHC	Reported
(Y. Cheng et al., 2012)	China	Cervical Cancer	70	38	51	89	1.587 (1.027–2.247)	0.013							IHC	K-M
(T. Liu et al., 2013)	China	Breast Cancer	60	75	48	123	10.723 (1.582–14.627)	<0.0001	10.831 (3.197–13.513)	<0.0001					IHC	Reported
(W.-F. Liu et al., 2012)	China	Gastric Cancer	>60	81	53	134	1.133 (0.977–1.784)	0							IHC	K-M

(Luo et al., 2012)	China	NPC	92	65	57	122	2.473 (1.185–5.160)	0.016							IHC	Reported
(Imajyo et al., 2012)	Japan	OSCC	60	11	124	135	1.461 (1.009–1.929)	0.03	1.549 (0.98–2.318)	0.022					IHC	K-M
(F. Richardson et al., 2012)	Canada	NSCLC	24	12	26	38	2.32 (1.09–4.94)	0.025							IHC	Reported
(Tseng et al., 2012)	Taiwan	HNSCC	112	15	37	52	3.071 (1.344–7.021)	0.008							IHC	Reported
(D. Chen et al., 2014)	Germany	RCC	>120	8	43	51							7.6 (1.7-34.4)	0.008	IHC	Reported
(Gu & Choi, 2014)	South Korea	Cholangiocarcinoma	180	18	67	85	4.344 (1.293–14.592)	0.017							IHC of TMA	Reported
(A. Kim et al., 2013)	South Korea	Intestinal Cancer	158	14	70	84	1.238 (0.965–1.705)	0.026							IHC	K-M
(Mao et al., 2013)	China	Cholangiocarcinoma	60	53	89	142	1.727 (1.002–2.803)	0.00							IHC	K-M
(Y. Nakashima et al., 2013)	Japan	ESCC	>60	20	81	101	1.271 (0.904–1.699)	0.016							IHC	K-M
(Sawant et al., 2014)	India	OSCC	184	52	175	227	1.938 (0.993–3.589)	0.0432							IHC	K-M
(W. Tian et al., 2013)	China	Leiomyosarcomas	>60	20	25	45	5.836 (1.315–13.880)	0.016							IHC	Reported
(Toiyama et al., 2013)	Japan	CRC	150	90	91	181	2.54 (1.47–4.38)	0.0008							RT-PCR	Reported
(Xu et al., 2013)	China	Pancreatic Cancer	>100	8	52	60	1.045 (0.997–1. 628)	0.01							IHC	K-M
(Yamashita et al., 2013)	Japan	Breast Cancer	240	32	50	82	3.33 (1.26–9.76)	0.015	3.27 (1.04–12.6)	0.043					RT-PCR	Reported
(X. Zhang et al., 2014)	China	NSCLC	60	118	62	56	1.374 (1.098–2.979)	0.021							IHC	K-M
(W. Zhao et al., 2013)	China	Gastric Cancer	55	14	129	143	8.146 (3.490–19.015)	< 0.001							IHC	Reported
(J et al., 2014)	China	Gastric Cancer	60	14	75	89	1.162 (0.936–1.469)	0.045							IHC	K-M
(Ding et al., 2014)	China	TSCC	140	18	32	50	1.71 (1.016–2.878)	0.044							IHC	Reported
(Gao et al., 2014)	China	CRC	60	58	136	194	1.596 (1.002–2.544)	0.026							IHC	K-M
(Goto et al., 2014)	Japan	OSCC	60	43	35	78	1.074 (0.998–1.219)	0.01							IHC	K-M
(Hao et al., 2014)	Canada	NPC	120	NM	NM	137			2.21 (1.11–4.38)	0.025					AQUA of TMA	Reported
(X.-Y. Huang et al., 2014)	China	Cholangiocarcinoma	120	78	62	140	1.081 (0.9274–1.397)	0.0385							IHC	K-M
(Kong et al., 2014)	China	NSCLC	60	17	51	68	2.596 (1.386–4.864)	0.003							IHC of TMA	Reported
(Sas-Korczynska et al., 2014)	Poland	Breast Cancer	302	2	26	28	2.710 (1. 293–3.613)	0.034							IHC	K-M

(Z.-G. Shi et al., 2015)	China	RCC	36	51	14	65	1.093 (0.493–2.421)	0.049							IHC	K-M
(Xiao, Liu, Fang, et al., 2015)	China	HCC	>60	59	47	106	1.38 (0.58–2.24)	0.084	1.59 (0.73–2.41)	0.042					IHC	Reported
(Yamazaki et al., 2014)	Japan	PDAC	100	44	69	113	2.833 (1.637–4.926)	<0.001							IHC	Reported
(Zhai et al., 2014)	China	HCC	60	32	81	113	2.025 (1.184–3.466)	0.01							IHC	Reported
(J. Zhao et al., 2014)	China	Bladder Cancer	180	30	91	121	0.278 (0.152–0.510)	0.001							IHC	Reported
(Che et al., 2015)	China	Lung Cancer	>70	22	81	103	1.918 (1.107–3.324)	0.02							IHC	Reported
(Dmello et al., 2016)	India	OSCC	200	47	23	70	5.834 (1.954–17.417)	0.002							IHC	K-M
(Y. Liu et al., 2015)	China	LSCC	60	68	20	88	1.769 (0.948–3.316)	0.0376							IHC	K-M
(H. Nakashima et al., 2015)	Japan	Lung Cancer	123,8	89	12	101	2.72 (1.23–6.52)	0.012	1.72 (1.00–2.99)	0.047					IHC	Reported
(Patel et al., 2015)	India	Breast Cancer	96	71	12	83	4.54 (1.74–11.84)	0.002	3.93 (1.88–8.22)	0.001					IHC	Reported
(Sowa et al., 2015)	Japan	Lung Cancer	129	50	189	239	1. 131 (1.064–1.26)	0.036							IHC	K-M
(Tanaka et al., 2015)	Japan	ESCC	>60	49	90	139	2.008 (1.191–3.384)	0.009							IHC	Reported
(Terashita et al., 2016)	Japan	Cholangiocarcinoma	170	44	58	102	1.117 (0.597–2.090)	0.049							IHC	Reported
(Xia et al., 2015)	China	NPC	93	78	46	124	3.364 (1.287–8.793)	0.013							IHC	Reported
(Xiao, Liu, Lu, et al., 2015)	China	CRC	81	59	46	105	2.038 (1.142–3.795)	0.01							IHC	Reported
(D. Zhou et al., 2016)	China	Breast Cancer	60	58	61	119	1.974 (1.032–3.462)	0.029	2.35 (0.994–3.826)	0.007					IHC	K-M
(Dong et al., 2016)	China	HCC	110	187	187	374	1.40 (1.05–1.87)	0.021	1.58 (1.18–2.13)	0.002					IHC	Reported
(Hu et al., 2016)	China	OSCC	91	32	39	71	1.342 (0.829–1.873)	0.032							IHC	K-M
(Z. Huang et al., 2016)	China	Colon Cancer	50	55	62	117	1.213 (0.483–3.047)	0.045							IHC	K-M
(Ingels et al., 2017)	Netherlands	RCC	91,8	39	104	143	1.026 (1.002–1.051)	0.032	1.035 (1.009–1.062)	0.007			1.05 (1.015-1.087)	0.005	IHC	Reported
(S. Liu et al., 2016)	China	OSCC	100	NM	NM	85	1.082 (0.639–1.832)	0.048							IHC	K-M
(Tadokoro et al., 2016)	Japan	NSCLC	60	40	68	108	3.86 (1.67–8.89)	0.0015							IHC	Reported
(W. Zhao et al., 2016)	China	Cervical Cancer	120	36	92	128	2.129 (1.077–4.207)	0.03							IHC	Reported

(J. Zhao et al., 2018)	China	Glioblastoma	24	121	58	179	1.122 (0.967–1.483)	0.042			1.35 (0.894–1.926)	0.037			IHC	K-M
(Y. Zhou et al., 2016)	China	NSCLC	95	94	59	153	1.776 (1.209–2.579)	0.003							IHC	Reported
(Zuo et al., 2016)	China	Larynx Cancer	60	47	10	57	1.244 (0.995–2.612)	0.0265							IHC	K-M
(D. Chen et al., 2018)	China	Gastric Cancer	72	57	45	102	1.189 (0.831–1.703)	0.043							IHC	K-M
(Choi et al., 2017)	South Korea	CRC	100	72	214	286	1.112 (1.0286–1.924)	0.0432							IHC	K-M
(Giró-Perafita et al., 2017)	Spain	Breast Cancer	>60	40	24	64			0.33 (0.11–1.00)	0.05					IHC	Reported
(J. Li et al., 2019)	China	NSCLC	60	76	58	134	7.292 (1.106–12.701)	<0.001							IHC	Reported
(J. Lin et al., 2017)	China	Cervical Cancer	89	35	95	130	8.386 (1.475–47.66)	0.012	11.213 (1.67–41.774)	0.003					IHC	Reported
(L.-G. Liu et al., 2017)	China	CRC	80	144	59	203	2.028 (1.021–4.029)	0.043	2.032 (1.106–3.734)	0.022					IHC	Reported
(P.-F. Liu et al., 2017)	Taiwan	TSCC	236	68	180	248			1.54 (1.01–2.34)	0.045			1.90 (1.26-2.87)	0.002	IHC	Reported
(Ni et al., 2017)	China	Prostate Cancer	>60	107	38	145	1.57 (1.017–2.509)	0.013							IHC	K-M
(Tsoukalas et al., 2017)	Greece	NSCLC	120	39	73	112	1.13 (0.78–1.65)	0.026							IHC of TMA	Reported
(W. Wang et al., 2018)	China	NPC	>80	39	31	70	2.576 (1.437–4.620)	0.001	1.572 (0.967–2.556)	0.038					IHC	K-M
(H. Wang et al., 2017)	China	Breast Cancer	76	64	81	145			4.15 (1.53–11.28)	0.005					IHC	Reported
(Yamanaka et al., 2018)	Japan	HCC	>72	12	74	86	Statistically not significant	0.108	1.167 (0.706–1.487)	0.015					IHC	K-M
(Yang et al., 2017)	China	NSCLC	180	112	74	186	1.252 (0.886–2.479)	0.02			1.305 (0.84–2.436)	0.017			IHC	K-M
(Aruga et al., 2018)	Japan	Lung Cancer	>60	42	61	103	1.868 (1.071–3.260)	0.028							IHC	Reported
(Kato et al., 2018)	Japan	OSCC	60	17	52	69	2.381 (0.784 – 7.230)	0.0261							IHC	Reported
(Ke et al., 2019)	China	Gastric Cancer	95	62	105	167	2.110 (1.360–3.274)	<0.001							IHC	Reported
(D. Li et al., 2018)	China	NSCLC	60	132	132	264	1.920 (1.306–2.822)	<0.001	2.338 (1.750–3.124)	<0.001					IHC	Reported
(H. Lin et al., 2018)	China	RCC	60	97	40	137	1.083 (0.993–1.891)	0.0376							IHC	K-M

(Sato et al., 2018)	Japan	ESCC	60	46	72	118	2.1704 (1.327–3.550)	<0.001							IHC	Reported
(Song et al., 2018)	China	NSCLC	84	67	131	198	1.121 (1.028–1.549)	0.022							IHC	K-M
(J.-Y. Wang et al., 2018)	China	Gastric Cancer	71	78	32	110	1.707 (1.033–2.819)	0.037							IHC	Reported
(Yin, Chen, Ye, et al., 2018)	China	Gastric Cancer	96	28	122	150	0.481 (0.274–0.843)	0.011							IHC	Reported
(Y. Zhang et al., 2018)	China	Gallbladder Cancer	66	17	88	105	2.934 (1.061–8.117)	0.038							IHC	Reported
(W. Zhao et al., 2019)	China	Gastric Cancer	120	198	50	248	2.167 (1.151–4.079)	0.017							IHC	Reported
(L. Chen et al., 2019)	China	Hepatoblastoma	73	13	34	47	2.347 (0.903–3.924)	0.0094							IHC	K-M
(Gong et al., 2019)	China	PDAC	60	27	33	60	4.936 (1.133–8.316)	0.004							IHC	Reported
(Imai et al., 2019)	Japan	Pancreatic Cancer	>60	8	28	36	1.1808 (0.971–2.183)	0.0433							IHC	K-M
(Karamagkiolas et al., 2019)	Greece	LSCC	120	46	23	69	3.59 (1.36–9.48)	0.01	2.2 (1.04–4.67)	0.039					IHC	Reported
(S. Liu et al., 2019)	China	Breast Cancer	162	68	72	140	1.095 (0.891–2.445)	0.0472							IHC	K-M
(L. Liu et al., 2019)	China	Ovarian cancer	50	26	13	39	2.161 (1.178–5.334)	0.0317	1.974 (1.147–5.053)	0.0434					IHC	Reported
(Maehira et al., 2019)	Japan	PDAC	103,9	24	43	67	2.305 (1.181–4.497)	0.014							IHC	Reported
(Qin et al., 2019)	China	HCC	60	33	47	80	1.123 (1.066–1.922)	0.0485							IHC	K-M
(C. Shi et al., 2019)	China	NSCLC	60	87	64	151	5.82 (3.644–9.295)	<0.001							IHC	Reported
(M. Wang et al., 2019)	USA	PDAC	205	14	106	120	2.55 (1.33–4.89)	0.01	2.50 (1.31–4.78)	0.016					IHC	Reported
(Wangmo et al., 2020)	China	OSCC	60	87	113	200							1.64 (1.12-2.41)	0.011	IHC of TMA	Reported
(H. Zhang et al., 2019)	China	Gastric Cancer	80	59	31	90	1.153 (0.790–1.682)	0.046							TMA	K-M
(Al-Maghrabi, 2020)	Saudi Arabia	CRC	>150	35	167	202	1.392 (0.861–1.646)	0.042	1.411 (0.846–1.624)	0.031					IHC	K-M
(Lobo et al., 2020)	Portugal	Bladder Cancer	>150	NM	NM	51			3.541 (1.402–8.943)	0.005					IHC	Reported
(Y. Tian et al., 2020)	China	Cervical Cancer	100	113	90	203	2.226 (1.387–3.573)	0.001							IHC	Reported
(H. Wang et al., 2020)	China	Gastric Cancer	96	37	70	107	3.337 (1.826–6.095)	<0.001							IHC	Reported
(Yao et al., 2020)	China	RCC	111	124	107	231	1.697 (1.067–2.699)	0.026							IHC	Reported

(Che et al., 2021)	China	Lung Cancer	80	21	77	98	1.850 (1.050–3.258)	0.033							IHC	Reported
(H. Cheng et al., 2021)	China	NPC	72	88	40	128	0.432 (0.169–0.988)	0.047	0.407 (0.189–0.878)	0.022	0.38 (0.168–0.859)	0.02			IHC	Reported
(C. Li & Ma, 2022)	China	ESCC	>100	116	69	185	1.51 (1.06–2.13)	0.022							IHC	Reported
(X. Zhang et al., 2022)	China	Endometrial Cancer	123	262	47	309	0.243 (0.116–0.512)	<0.001							IHC	Reported

Abbreviations: OS, overall survival; DSS, disease specific survival; RFS, recurrence-free survival; DFS, disease-free survival; MFS, metastasis-free survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; qRT-PCR, quantitative reverse transcription polymerase chain reaction; TMA, tissue microarray analysis; IHC, immunohistochemistry; AQUA, automated quantitative immunohistochemistry; NM, not mentioned; K-M, Kaplan-Meier plot; RCC, renal cell carcinoma; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; SqCC or SCC, squamous cell carcinoma; TSCC, thymic squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; LSCC, laryngeal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; and OSCC, oral squamous cell carcinoma.

4.2. Impact of Elevated Vimentin Expression on Survival Outcomes in Cancer

A total of 103 studies were analyzed for overall survival (OS), revealing a statistically significant association between elevated vimentin expression and poor OS (common-effect inverse-variance model: pooled HR = 1.036; 95% CI: 1.015–1.058; p = 0.000), accompanied by moderately high heterogeneity (I^2 = 73.4%; P_h = 0.000) (**Figure 5a**).

4.3. Elevated Vimentin Expression Correlates with Cancer Recurrence and Progression

To examine the link between vimentin expression and cancer recurrence or relapse, studies on recurrence-free survival (RFS) and disease-free survival (DFS) were combined, encompassing a total of 25 studies. The analysis revealed that increased vimentin expression is significantly associated with cancer recurrence (pooled HR = 1.041; 95% CI: 1.015–1.067; p = 0.000), with a similar level of heterogeneity (I^2 = 73.6%; P_h = 0.000) (**Figure 5b**). Four studies focused on metastasis-free survival (MFS) and progression-free survival (PFS) showed a statistically significant relationship between increased vimentin expression and adverse MFS and PFS outcomes (common-effect inverse-variance model: pooled HR = 1.070; 95% CI: 0.440–1.700; p = 0.001), with heterogeneity reaching a moderately high level (I^2 = 78.4%; P_h = 0.003) (**Figure 5c**). Lastly, eight studies assessing disease-specific survival (DSS) identified a statistically significant correlation between elevated vimentin expression and poorer DSS (common-effect inverse-variance model: pooled HR = 1.055; 95% CI: 1.019–1.091; p = 0.000), with moderate heterogeneity (I^2 = 51.0%; P_h = 0.047) (**Figure 5d**).

4.4. Subgroup Analyses of Vimentin Overexpression and Survival Outcomes Across Cancer Types, Geographic Regions, and Socioeconomic Factors

Subgroup analyses were performed based on the types of cancer by primary anatomical site, the endocrine gland neoplasms, the types of squamous cell carcinoma, the data extraction method, the income of the country where healthcare is

provided and the geography (**Figure 6**). When the studies were classified based on major cancer types (according to NCBI's medical subject headings (MeSH) (NCBI Resource Coordinators, 2016) (https://www.ncbi.nlm.nih.gov/mesh/), a significant association was found between vimentin overexpression and poorer OS in solid cancers, such as breast neoplasms (common-effect inverse-variance model: pooled HR = 1.997; 95% CI: 1.538–2.455; p = 0.000), muscular system neoplasms where the worst association was detected (common-effect inverse-variance model: pooled HR = 5.836; 95% CI: -0.447–12.118; p = 0.069), digestive system neoplasms (common-effect inverse-variance model: pooled HR = 1.175; 95% CI: 1.100–1.250; p = 0.000), head and neck neoplasms (common-effect inverse-variance model: pooled HR = 1.058; 95% CI: 0.962-1.153; p = 0.000), nervous system neoplasms (common-effect inverse-variance model: pooled HR = 1.155; 95% CI: 0.914–1.396; p = 0.000), respiratory system neoplasms (common-effect inverse-variance model: pooled HR = 1.187; 95% CI: 1.102–1.273; p = 0.000) and urogenital system neoplasms (common-effect inverse-variance model: pooled HR = 1.005; 95% CI: 0.981–1.029; p = 0.000).

Notably, the heterogeneity was significantly reduced within individual cancer types (**Figure 6a**). Interestingly, in the subgroup analysis based on the host country's income, a statistically significant worse OS was observed for the lower-middle income subgroup (common-effect inverse-variance model: pooled HR = 2.195; 95% CI: 0.955–3.436; p = 0.001) than the high (common-effect inverse-variance model: pooled HR = 1.045; 95% CI: 1.022–1.067; p = 0.000) and upper-middle (common-effect inverse-variance model: pooled HR = 0.960; 95% CI: 0.894–1.027; p = 0.000) subgroups (**Figure 6b)**.

In the subgroup analysis based on geography, the survival rates, which are all statistically significant, are listed from worst to best in North America (common-effect inverse-variance model: pooled HR = 1.629; 95% CI: 1.199–2.059; p = 0.000), the Middle East (common-effect inverse-variance model: pooled HR = 1.478; 95% CI: 1.114–1.842; p = 0.000), Asia (common-effect inverse-variance model: pooled HR = 1.050; 95% CI: 1.005–1.095; p = 0.000) and Europe (common-effect inverse-variance model: pooled HR = 1.028; 95% CI: 1.004–1.053; p = 0.000) (**Figure 7a**).

Another subgroup analysis was made by comparing studies based on the data extraction method, in which HR data was reported, and the studies where HR data was

extracted from the Kaplan–Meier curves (**Figure 7b**). In a stratified analysis based on the data extraction method, vimentin demonstrated significant prognostic value regardless of the data source. The hazard ratio (HR) reported in the articles (common-effect inverse-variance model: combined HR = 1.011; 95% CI: 0.987–1.034; p = 0.000) and extracted from the survival curves (common-effect inverse-variance model: combined HR = 1.036; 95% CI: 1.015–1.058; p = 0.000) consistently showed significant results (**Figure 7b**).

Forest plots of combined analyses for overall survival (OS) associated with vimentin expression in different squamous cell carcinoma and endocrine-related cancer groups are shown respectively in **Figure 8a** and **Figure 8b**. In the SCC subgroup analysis, vimentin overexpression showed a statistically significant correlation with poor survival (common-effect inverse-variance model: pooled HR = 1.126; 95% CI: 1.033–1.219; p = 0.000). Among the SCC types, HNSCC is ostensibly the cancer type with the highest HR in this subgroup analysis (common-effect inverse-variance model: pooled HR = 3.071; 95% CI: 1.344–7.021; p = 0.034). In the endocrine-related cancers subgroup a statistically significant relationship between elevated vimentin expression and poor OS (common-effect inverse-variance model: pooled HR = 1.013; 95% CI: 0.990–1.037; p = 0.000) was also found.

Figure 5. Forest plots of the combined analyses on the association between survival and vimentin expression. Forest plot for (a) overall survival (OS) analysis, (b) recurrence-free survival (RFS) and disease-free survival (DFS) analysis, (c) metastasis-free survival (MFS) and progression-free survival (PFS) analysis, and (d) disease-specific survival analysis (DSS).

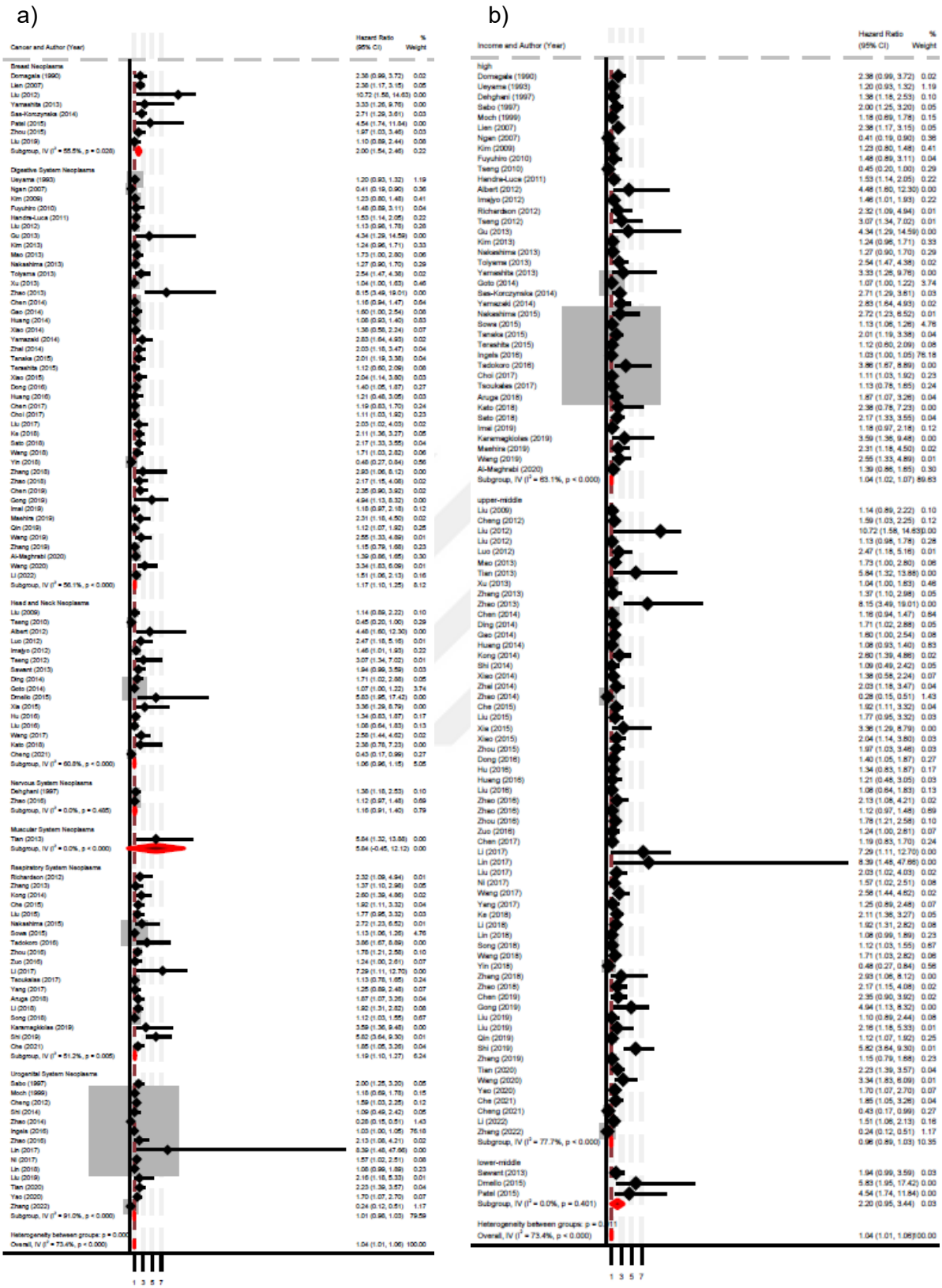


Figure 6. Forest plots of combined analyses for overall survival (OS) associated with vimentin expression in the subgroup based on (a) different types of cancers, and (b) the host country's income.

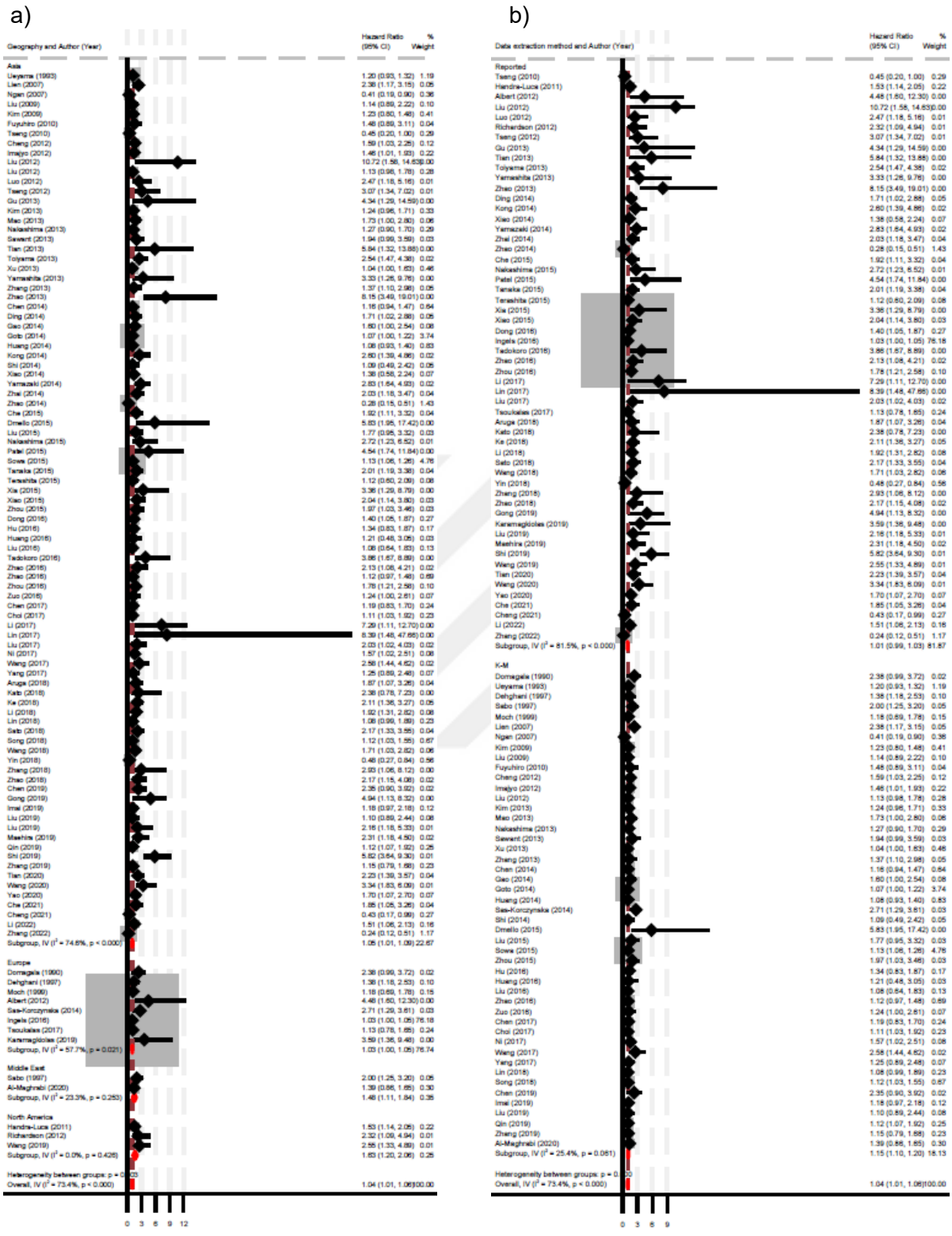


Figure 7. Forest plots of combined analyses for overall survival (OS) associated with vimentin expression in the subgroup based on (a) geography, and (b) different data extraction methods.

a)

b)

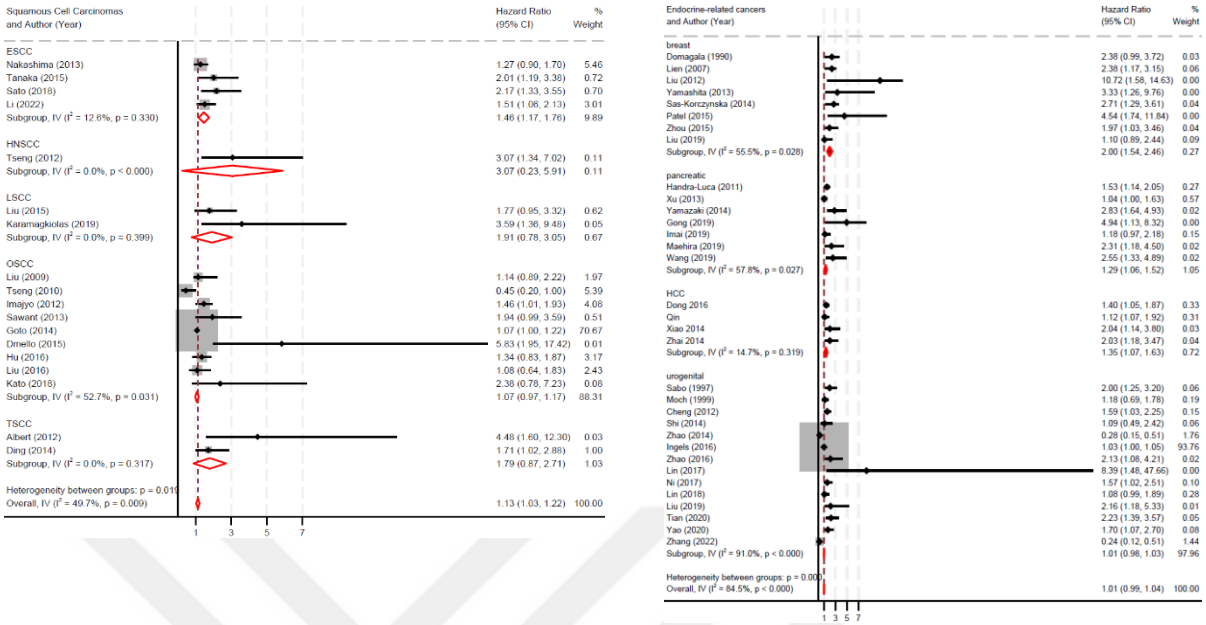


Figure 8. Forest plots of combined analyses for overall survival (OS) associated with vimentin expression in the subgroup of (a) squamous cell carcinomas (SSC) and (b) endocrine-related cancers.

4.5. Publication Bias

Publication bias was detected by Begg's funnel plot and Egger's test. The Begg's funnel plot of OS (**Figure 9a**), DFS/RFS (**Figure 9b**), and DSS (**Figure 9d**) were asymmetric and the p value of Egger's test were less than 0.05 (p = 0.000, p = 0.001, p = 0.003 respectively), indicating potential bias. However, there was no clear evidence of potential bias based on Begg's funnel plot of MFS/PFS (**Figure 9c**). Additionally, the p value of Egger's test was greater than 0.05, indicating no potential bias for MFS/PFS (p = 0.159).

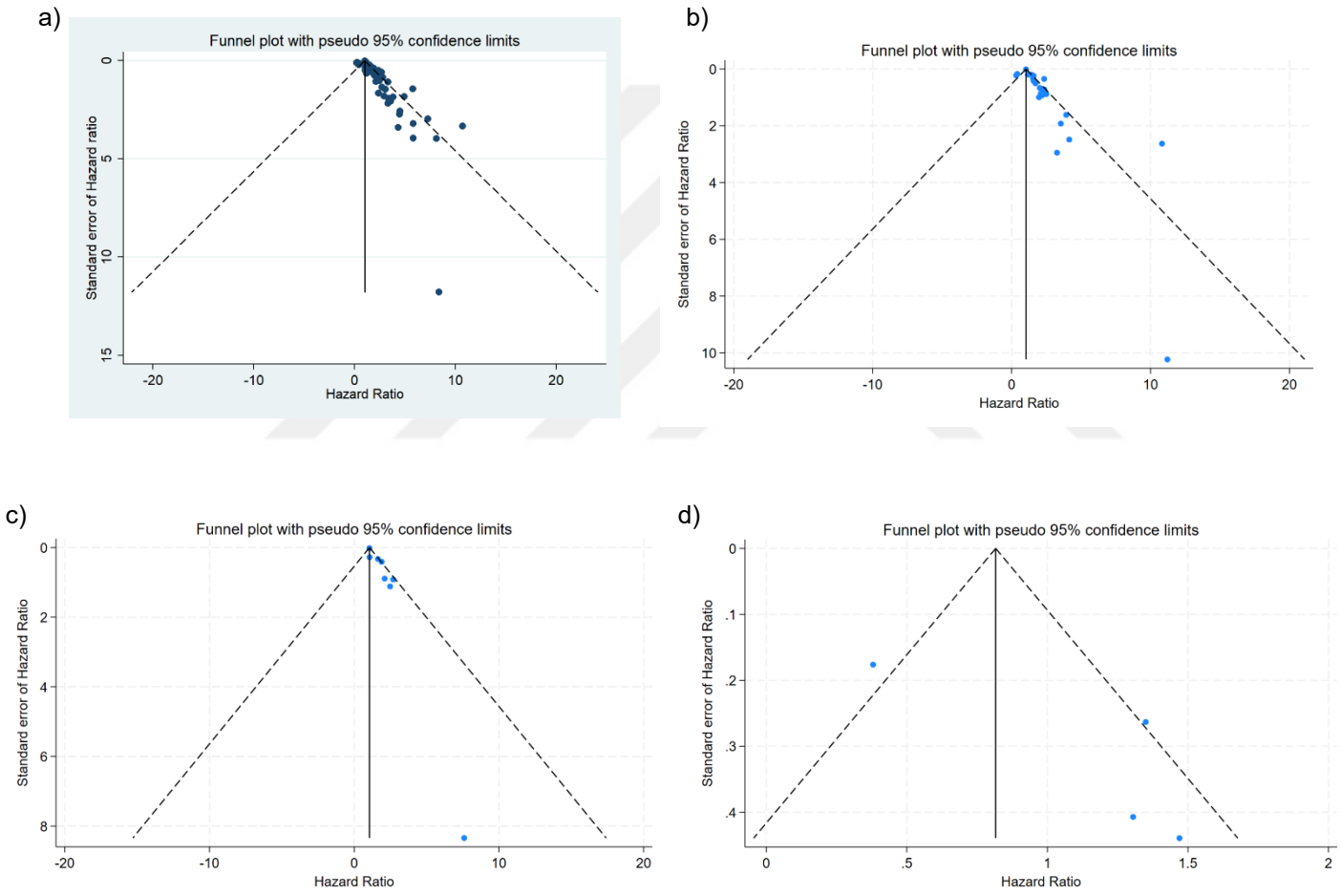
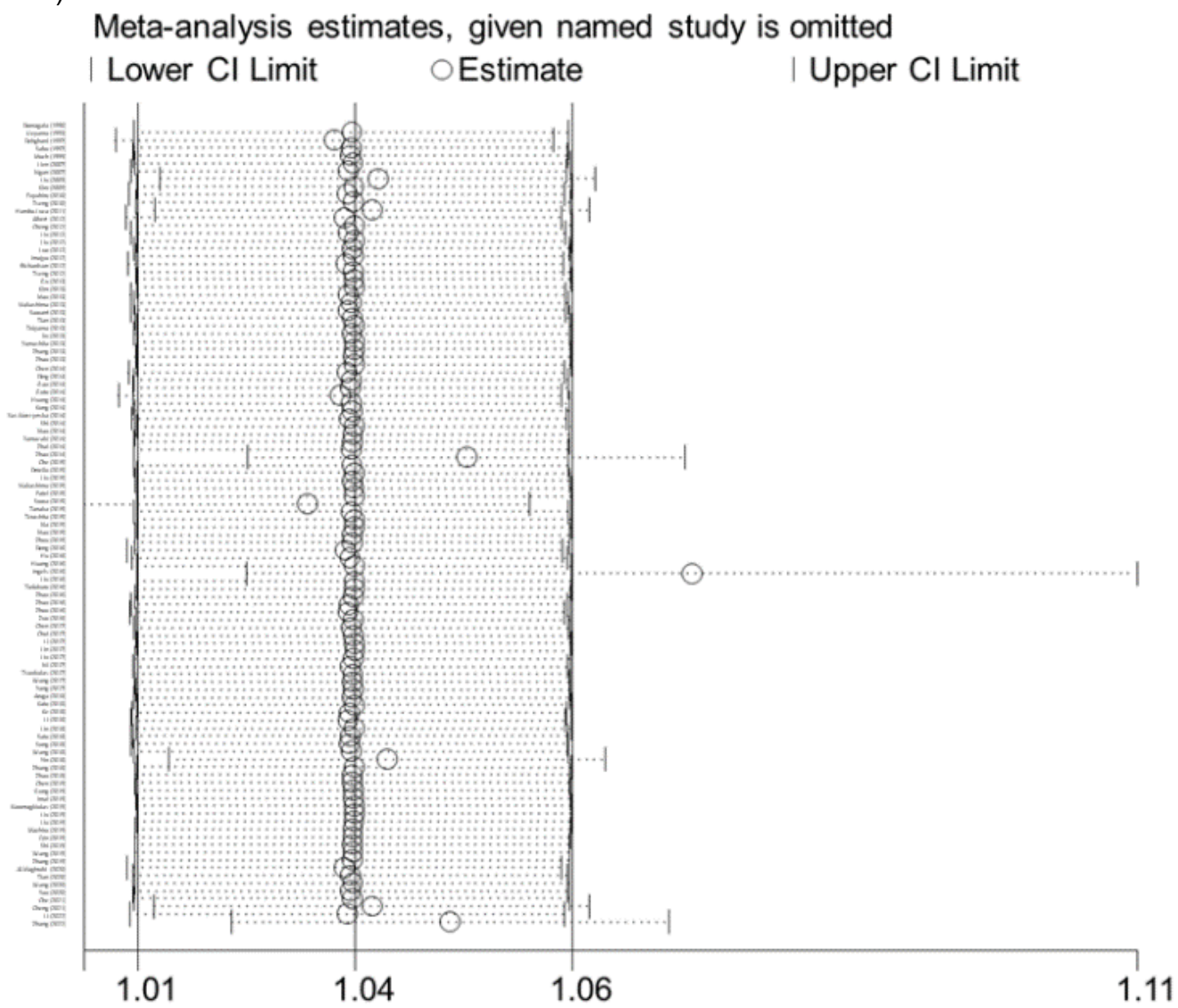


Figure 9. Begg's funnel plots illustrating publication bias. Begg's funnel plot for (a) overall survival (OS), (b) recurrence-free survival (RFS) and disease-free survival (DFS), (c) disease-specific survival (DSS), (d) metastasis-free survival (MFS) and progression-free survival (PFS).Each dot represents an individual study.

4.6. Sensitivity Analysis

Sensitivity analyses showed that the results remained consistent regardless of the inclusion of any individual study (**Figure 10**). In other words, no single study had an impact on the pooled HR or 95% CI.

a)



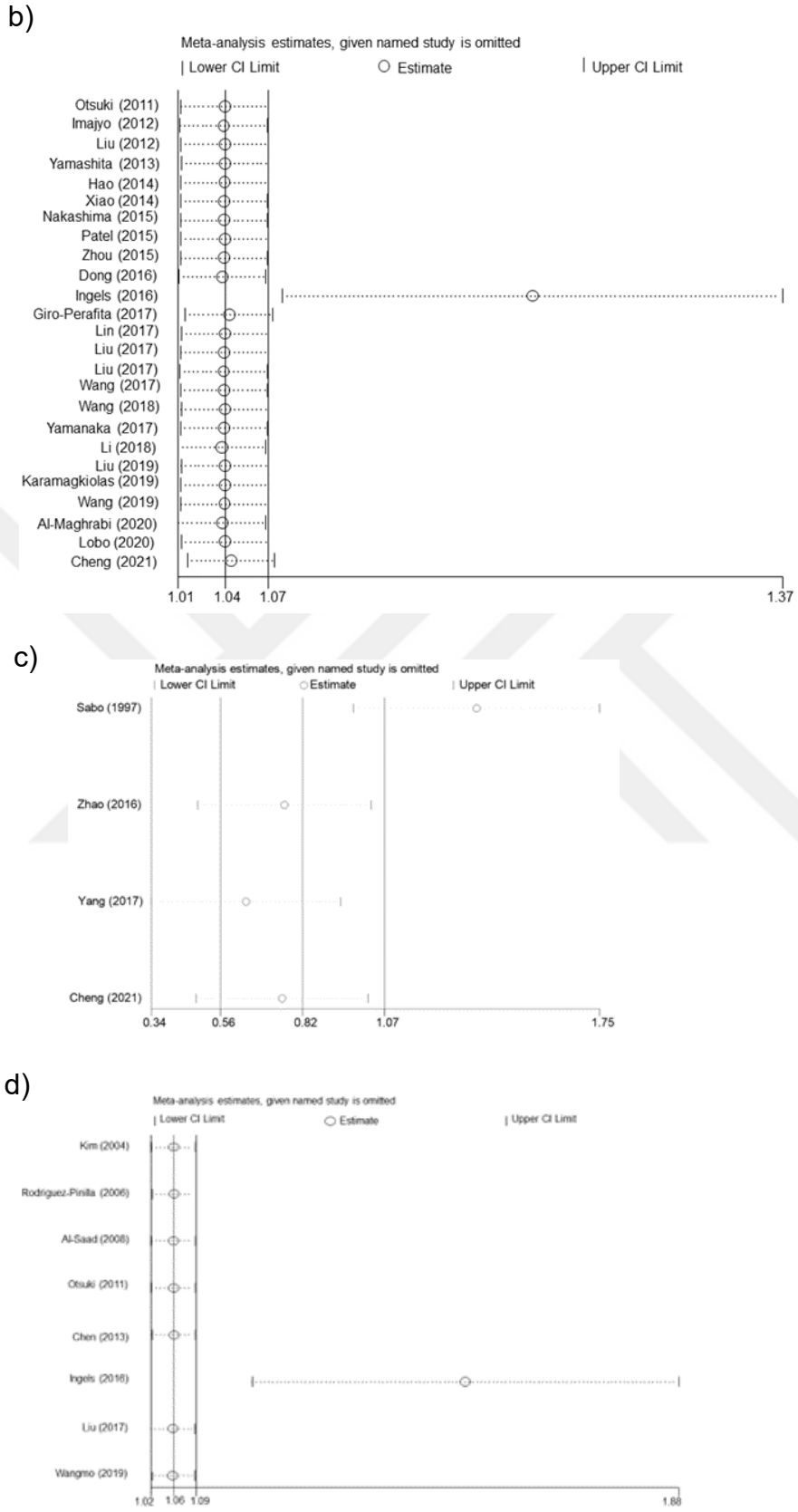


Figure 10. Sensitivity analysis of each eligible study. (a) OS individual studies, (b) MFS/PFS individual studies, (c) DSS individual and (d) DFS/RFS.

5. DISCUSSION

As a major component of intermediate filaments within the cytoskeleton, vimentin is widely expressed in mesenchymal-origin cells, such as fibroblasts, endothelial cells, smooth muscle cells, leukocytes, and several other cell types and plays a crucial role in maintaining cell shape and providing resistance against mechanical stress (Santos et al., 2008). In addition, vimentin expression was found in the CRC (colorectal cancer) tumour stroma, which was suggested to be useful in identifying CRC patients with a poor prognosis (Ngan et al., 2007). Otsuki et al. reported that vimentin mRNA expression was associated with recurrence or distant metastasis and poor survival in gastric cancer; however, immunohistochemical detection of vimentin expression was limited to the cancer stroma (Otsuki et al., 2011).

The intricate role of the vimentin molecule extends beyond its structural contributions to cellular integrity, resonating profoundly in the landscape of cancer biology. In a myriad of cancer types, upregulation of vimentin represents a common denominator, marking a critical turning point in disease progression.

Numerous studies suggest that the presence of increased levels of vimentin in various cancer tissues can serve as a prognostic marker. High vimentin expression has been associated with poor clinical outcomes, including reduced survival rates and increased likelihood of metastasis. Zhao et al. conducted a study indicating that vimentin holds the potential to function as an independent predictor for both the progression and survival of bladder cancer (Zhao et al., 2014). In the context of breast cancer, Patel et al. and Zhou et al. found that vimentin expression serves as a robust indicator of biologically aggressive tumors, predicting decreased disease-free survival (DFS) and overall survival (OS) (Patel et al., 2015; D. Zhou et al., 2016). A multivariate analysis by Lin and colleagues further supports vimentin's role as an independent marker for survival among cervical cancer patients (Lin et al., 2017). Additionally, the expression of vimentin in tumors has been demonstrated to offer valuable prognostic insights for individuals diagnosed with localized renal cell carcinoma (Sabo et al., 1997).

Liu and coworkers identified vimentin as a promising prognosis marker for metastatic OSCC. It was found that upregulated vimentin is among the most

differentially expressed genes in metastatic versus non-metastatic OSCC cells. They revealed that the knockdown of vimentin expression resulted in suppressed migration and invasion activities of HN12 cells, and higher vimentin expression was associated with lymph node metastasis and poor prognosis in clinical OSCC sample analysis. Therefore, high vimentin expression could serve as a risk marker for predicting cervical lymph node metastasis and poor prognosis (Liu et al., 2016).

Vimentin is a well-researched molecule in urogenital system neoplasms, where elevated levels of vimentin are suggested as potential independent predictors for cancer prognosis (Cheng et al., 2012; Shi et al., 2015; Zhao et al., 2014). It is widely recognized that renal sarcoma and sarcomatoid variants of RCC, which are associated with poor prognosis, exhibit expression of the mesenchymal intermediate filament vimentin, as demonstrated by IHC staining (Sella et al., 1987). Sabo and colleagues demonstrated that univariate analysis of patient survival and tumor recurrence revealed a statistically significant link between vimentin-positive tumors and unfavorable patient outcomes. The study also reported that combining tumor vimentin expression with histological grade offered a more accurate prediction of prognosis and was identified as the most reliable independent prognostic factor for survival in multivariate analysis (Sabo et al., 1997). In another study, Donhuijsen and Schulz indicated that tumors positive for vimentin had a higher progression rate compared to vimentin-negative tumors in a cohort of 93 RCC patients (Donhuijsen & Schulz, 1989). In a study by Moch et al, over 300 RCC cases with clinical follow-up data were examined using a tumor array. The findings not only reinforced the prognostic significance of vimentin expression in RCC, but also indicated through multivariate statistical analysis that vimentin may serve as an independent prognostic marker in clear cell RCC (Moch et al., 1999).

Moreover, studies on bladder cancer (BCa) have consistently shown that mesenchymal features correlate significantly with a higher likelihood of disease recurrence, metastatic spread, tumor progression, and poorer prognosis, including reduced survival and resistance to treatment (Liu et al., 2015; McConkey et al., 2009; Zhao et al., 2014). Lobo et al. found that both vimentin mRNA and protein expression levels were significantly higher in muscle-invasive bladder cancer (MIBC) compared to non-muscle-invasive bladder cancer (NMIBC), indicating an association of vimentin

with advanced stages of cancer. In the study, the increased expression of vimentin protein in more aggressive tumor samples underscores the influence of EMT in acquiring a more aggressive cancer phenotype. Importantly, translating these findings to patient outcomes, they observed that NMIBC patients with higher vimentin expression had shorter DFS (Lobo et al., 2020).

Moreover, vimentin plays a role in cell cycle regulation and adhesion, highlighting its significance in cancer development and progression. Intriguingly, vimentin has been found to form a complex with TP53 in the cytoplasm, suppressing TP53 from translocating to the nucleus and inhibiting TP53's apoptosis-promoting function; this indicates that TP53 is also important in the EMT pathway. Lin and colleagues demonstrated that the expression of vimentin, TP53, and podoplanin are linked to the survival rates of cervical cancer patients, suggesting these proteins as potential biomarkers for diagnosing and treating cervical cancer. The study also showed that vimentin could be an independent prognostic marker for cervical cancer patients undergoing primary surgery (Lin et al., 2017).

Vimentin serves not only as a scaffolding protein but also mediates various signaling pathways and cellular processes (Satelli & Li, 2011). Perlson et al. demonstrated that vimentin interacts with phosphorylated Erk (pErk), a MAP kinase, and protects it from dephosphorylation. The study reports that pErk binds to the second coiled-coil domain of vimentin in a calcium-dependent manner. As a result, vimentin stabilizes pErk by shielding it from dephosphorylation through calcium-dependent steric hindrance, thus facilitating the long-distance transport of phosphorylated Erk within the cell (Perlson et al., 2006). On the other hand, phosphorylated vimentin has been shown to interact with the 14-3-3 protein, preventing the assembly of Raf-14-3-3 and similar complexes. This suggests that vimentin regulates 14-3-3 complexes and controls various intracellular signaling and cell cycle pathways by modulating the availability of 14-3-3 (Tzivion et al., 2000). Zhu and colleagues also found that AKT1 kinase binds to phosphorylated vimentin, shielding it from caspase-induced proteolysis. This binding results in enhanced cell motility and invasion in soft-tissue sarcoma cells (Zhu et al., 2011).

In this study, we performed an updated and comprehensive meta-analysis on the prognostic significance of vimentin in various human cancers. By implementing a

strict inclusion and exclusion criteria, we included 115 eligible studies, a sufficiently large number for a robust meta-analysis. Previous meta-analyses on the association of vimentin with clinical outcomes included far less studies encompassing much less patients. Also these studies have concentrated on specific cancer types such as gastric cancer (Yin, Chen, & Yang, 2018), colorectal cancer (Du et al., 2018) and nasopharyngeal carcinoma (Lu et al., 2019).

We also demonstrated that elevated vimentin expression is correlated with poor overall survival (OS), disease-free survival (DFS) or recurrence-free survival (RFS), metastasis-free survival (MFS) or progression-free survival (PFS), and disease-specific survival (DSS). In the subgroup analysis based on cancer type, vimentin was found to be a significant predictor of worse prognosis for various cancers, including solid neoplasms such as those in the breast, nervous system, urogenital system, head and neck, muscular system, digestive system, and respiratory system. Additionally, we elaborated on the meta-analysis findings and further supported our hypotheses by analyzing survival information from other cancer types. Specifically, we examined subgroups of squamous cell carcinomas and endocrine-related cancers. There was a strong relationship between vimentin overexpression and poor overall survival (OS) in cancers such as esophageal squamous cell carcinoma (ESCC), head and neck squamous cell carcinoma (HNSCC), laryngeal squamous cell carcinoma (LSCC), oral squamous cell carcinoma (OSCC), and tongue squamous cell carcinoma (TSCC) from the squamous cell carcinoma subgroup, as well as breast cancer, hepatocellular carcinoma (HCC), pancreatic cancer, and urogenital cancers from the endocrine-related cancers subgroup.

Interestingly, in the subgroup analysis based on the income level of the country where healthcare is provided, a statistically significant worse overall survival (OS) was observed in the lower-middle income subgroup compared to the high and upper-middle income subgroups. In the subgroup analysis of data extraction methods, where we compared studies that reported hazard ratios (HR) with those that only included Kaplan-Meier (KM) curves, vimentin demonstrated significant prognostic value regardless of the data source.

6. CONCLUSION AND FUTURE ASPECTS

This study highlights the significant prognostic value of vimentin across various cancers. Through a comprehensive meta-analysis of 115 studies, we have demonstrated that elevated vimentin expression is consistently associated with poor overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), metastasis-free survival (MFS), progression-free survival (PFS), and disease-specific survival (DSS). The association is particularly pronounced in solid tumors, including those in the breast, nervous system, urogenital system, head and neck, muscular system, digestive system, and respiratory system. Additionally, vimentin was identified as a critical predictor of poor prognosis in specific cancer subtypes, such as squamous cell carcinomas and endocrine-related cancers. The consistency of vimentin's prognostic significance across diverse cancer types underscores its potential as a robust biomarker in clinical oncology.

Future research should delve deeper into the molecular mechanisms by which vimentin contributes to cancer progression and metastasis. Understanding these mechanisms could pave the way for developing targeted therapies aimed at mitigating vimentin's impact on tumor aggressiveness. Additionally, further studies are needed to validate vimentin as a therapeutic target, exploring the potential for vimentin inhibitors to improve clinical outcomes for patients with high vimentin-expressing tumors. Lastly, the integration of vimentin expression analysis into personalized treatment strategies could enhance the precision of cancer care, tailoring interventions to improve survival rates for patients across a spectrum of malignancies.

7. REFERENCES

Albert, S., Hourseau, M., Halimi, C., Serova, M., Descatoire, V., Barry, B., Couvelard, A., Riveiro, M. E., Tijeras-Raballand, A., de Gramont, A., Raymond, E., & Faivre, S. (2012). Prognostic value of the chemokine receptor CXCR4 and epithelial-to-mesenchymal transition in patients with squamous cell carcinoma of the mobile tongue. *Oral Oncology*, *48*(12), 1263–1271. https://doi.org/10.1016/j.oraloncology.2012.06.010

Al-Maghrabi, J. (2020). Vimentin immunoexpression is associated with higher tumor grade, metastasis, and shorter survival in colorectal cancer. *International Journal of Clinical and Experimental Pathology*, *13*(3), 493–500.

Al-Saad, S., Al-Shibli, K., Donnem, T., Persson, M., Bremnes, R. M., & Busund, L.-T. (2008). The prognostic impact of NF-kappaB p105, vimentin, E-cadherin and Par6 expression in epithelial and stromal compartment in non-small-cell lung cancer. *British Journal of Cancer*, *99*(9), 1476–1483. https://doi.org/10.1038/sj.bjc.6604713

Aruga, N., Kijima, H., Masuda, R., Onozawa, H., Yoshizawa, T., Tanaka, M., Inokuchi, S., & Iwazaki, M. (2018). Epithelial-mesenchymal Transition (EMT) is Correlated with Patient's Prognosis of Lung Squamous Cell Carcinoma. *The Tokai Journal of Experimental and Clinical Medicine*, *43*(1), 5–13.

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, *50*(4), 1088–1101.

Brooke, B. S., Schwartz, T. A., & Pawlik, T. M. (2021). MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. *JAMA Surgery*, *156*(8), 787–788. https://doi.org/10.1001/jamasurg.2021.0522

Carnero, A., & Lleonart, M. (2016). The hypoxic microenvironment: A determinant of cancer stem cell evolution. *BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology*, *38 Suppl 1*, S65-74. https://doi.org/10.1002/bies.201670911

Che, J., Wang, J., Li, H., Zhen, H., Shang, K., Yang, Y., & Cao, B. (2021). Decreased expression of Dlg5 is associated with a poor prognosis and epithelial-mesenchymal transition in squamous cell lung cancer. *Journal of Thoracic Disease*, *13*(5), 3115–3125. https://doi.org/10.21037/jtd-21-752

Che, J., Yang, Y., Xiao, J., Zhao, P., Yan, B., Dong, S., & Cao, B. (2015). Decreased expression of claudin-3 is associated with a poor prognosis and EMT in completely resected squamous cell lung carcinoma. *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine*, *36*(8), 6559–6568. https://doi.org/10.1007/s13277-015-3350-1

Chen, D., Gassenmaier, M., Maruschke, M., Riesenberg, R., Pohla, H., Stief, C. G., Zimmermann, W., & Buchner, A. (2014). Expression and prognostic significance of a comprehensive epithelial-mesenchymal transition gene set in renal cell carcinoma. *The Journal of Urology*, *191*(2), 479–486. https://doi.org/10.1016/j.juro.2013.08.052

Chen, D., Zhou, H., Liu, G., Zhao, Y., Cao, G., & Liu, Q. (2018). SPOCK1 promotes the invasion and metastasis of gastric cancer through Slug-induced epithelial-mesenchymal transition. *Journal of Cellular and Molecular Medicine*, *22*(2), 797–807. https://doi.org/10.1111/jcmm.13357

Chen, J. H., Vercamer, C., Li, Z., Paulin, D., Vandenbunder, B., & Stehelin, D. (1996). PEA3 transactivates vimentin promoter in mammary epithelial and tumor cells. *Oncogene*, *13*(8), 1667–1675.

Chen, L., Tian, X., Gong, W., Sun, B., Li, G., Liu, D., Guo, P., He, Y., Chen, Z., Xia, Y., Song, T., & Guo, H. (2019). Periostin mediates epithelial-mesenchymal transition through the MAPK/ERK pathway in hepatoblastoma. *Cancer Biology & Medicine*, *16*(1), 89–100. https://doi.org/10.20892/j.issn.2095-3941.2018.0077

Cheng, H., Zhou, L., Long, Y., Xiang, J., & Chen, L. (2021). MACC1 Is Associated With Epithelial-Mesenchymal Transition and Can Predict Poor Prognosis in Nasopharyngeal Carcinoma. *Frontiers in Oncology*, *11*, 644120. https://doi.org/10.3389/fonc.2021.644120

Cheng, Y., Zhou, Y., Jiang, W., Yang, X., Zhu, J., Feng, D., Wei, Y., Li, M., Yao, F., Hu, W., Xiao, W., & Ling, B. (2012). Significance of E-cadherin, β-catenin, and vimentin expression as postoperative prognosis indicators in cervical squamous cell carcinoma. *Human Pathology*, *43*(8), 1213–1220. https://doi.org/10.1016/j.humpath.2011.08.025

Choi, J. E., Bae, J. S., Kang, M. J., Chung, M. J., Jang, K. Y., Park, H. S., & Moon, W. S. (2017). Expression of epithelial-mesenchymal transition and cancer stem cell

markers in colorectal adenocarcinoma: Clinicopathological significance. *Oncology Reports*, *38*(3), 1695–1705. https://doi.org/10.3892/or.2017.5790

Clarke, M. (2000). The QUORUM statement. *Lancet (London, England)*, *355*(9205), 756–757. https://doi.org/10.1016/S0140-6736(05)72172-3

Cochran, W. G. (1950). The Comparison of Percentages in Matched Samples. *Biometrika*, *37*(3/4), 256. https://doi.org/10.2307/2332378

Cordero, C. P., & Dans, A. L. (2021). Key concepts in clinical epidemiology: Detecting and dealing with heterogeneity in meta-analyses. *Journal of Clinical Epidemiology*, *130*, 149–151. https://doi.org/10.1016/j.jclinepi.2020.09.045

Crystal, R. G., Randell, S. H., Engelhardt, J. F., Voynow, J., & Sunday, M. E. (2008). Airway epithelial cells: Current concepts and challenges. *Proceedings of the American Thoracic Society*, *5*(7), 772–777. https://doi.org/10.1513/pats.200805-041HR

Danielsson, F., Peterson, M. K., Caldeira Araújo, H., Lautenschläger, F., & Gad, A. K. B. (2018). Vimentin Diversity in Health and Disease. *Cells*, *7*(10), 147. https://doi.org/10.3390/cells7100147

Das, S., Dey, M. K., Devireddy, R., & Gartia, M. R. (2023). Biomarkers in Cancer Detection, Diagnosis, and Prognosis. *Sensors (Basel, Switzerland)*, *24*(1), 37. https://doi.org/10.3390/s24010037

de Moraes, F. C. A., Pereira, C. R. M., Sano, V. K. T., Laia, E. A. D., Stecca, C., & Burbano, R. M. R. (2024). Do proton pump inhibitors affect the effectiveness of cyclin-dependent kinase 4/6 inhibitors in advanced HR positive, HER2 negative breast cancer? A meta-analysis. *Frontiers in Pharmacology*, *15*, 1352224. https://doi.org/10.3389/fphar.2024.1352224

Dehghani, F., Schachenmayr, W., Laun, A., & Korf, H. W. (1998). Prognostic implication of histopathological, immunohistochemical and clinical features of oligodendrogliomas: A study of 89 cases. *Acta Neuropathologica*, *95*(5), 493–504. https://doi.org/10.1007/s004010050830

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, *7*(3), 177–188. https://doi.org/10.1016/0197-2456(86)90046-2

DerSimonian, R., & Laird, N. (2015). Meta-analysis in clinical trials revisited. *Contemporary Clinical Trials*, *45*(Pt A), 139–145. https://doi.org/10.1016/j.cct.2015.09.002

Dettori, J. R., Norvell, D. C., & Chapman, J. R. (2022). Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. *Global Spine Journal*, *12*(7), 1624–1626. https://doi.org/10.1177/21925682221110527

Ding, L., Zhang, Z., Shang, D., Cheng, J., Yuan, H., Wu, Y., Song, X., & Jiang, H. (2014). α-Smooth muscle actin-positive myofibroblasts, in association with epithelial-mesenchymal transition and lymphogenesis, is a critical prognostic parameter in patients with oral tongue squamous cell carcinoma. *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, *43*(5), 335–343. https://doi.org/10.1111/jop.12143

Dmello, C., Sawant, S., Alam, H., Gangadaran, P., Tiwari, R., Dongre, H., Rana, N., Barve, S., Costea, D. E., Chaukar, D., Kane, S., Pant, H., & Vaidya, M. (2016). Vimentin-mediated regulation of cell motility through modulation of beta4 integrin protein levels in oral tumor derived cells. *The International Journal of Biochemistry & Cell Biology*, *70*, 161–172. https://doi.org/10.1016/j.biocel.2015.11.015

Domagala, W., Lasota, J., Dukowicz, A., Markiewski, M., Striker, G., Weber, K., & Osborn, M. (1990). Vimentin expression appears to be associated with poor prognosis in node-negative ductal NOS breast carcinomas. *The American Journal of Pathology*, *137*(6), 1299–1304.

Dong, Q., Zhu, X., Dai, C., Zhang, X., Gao, X., Wei, J., Sheng, Y., Zheng, Y., Yu, J., Xie, L., Qin, Y., Qiao, P., Zhou, C., Yu, X., Jia, H., Ren, N., Zhou, H., Ye, Q., & Qin, L. (2016). Osteopontin promotes epithelial-mesenchymal transition of hepatocellular carcinoma through regulating vimentin. *Oncotarget*, *7*(11), 12997–13012. https://doi.org/10.18632/oncotarget.7016

Donhuijsen, K., & Schulz, S. (1989). Prognostic significance of vimentin positivity in formalin-fixed renal cell carcinomas. *Pathology, Research and Practice*, *184*(3), 287–291. https://doi.org/10.1016/S0344-0338(89)80088-3

Downes, M. J., Brennan, M. L., Williams, H. C., & Dean, R. S. (2016). Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open*, *6*(12), e011458. https://doi.org/10.1136/bmjopen-2016-011458

Du, L., Li, J., Lei, L., He, H., Chen, E., Dong, J., & Yang, J. (2018). High Vimentin Expression Predicts a Poor Prognosis and Progression in Colorectal Cancer: A Study with Meta-Analysis and TCGA Database. *BioMed Research International*, *2018*, 6387810. https://doi.org/10.1155/2018/6387810

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)*, *315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Eibauer, M., Weber, M. S., Turgay, Y., Sivagurunathan, S., Goldman, R. D., & Medalia, O. (n.d.). *The molecular architecture of vimentin filaments*.

Evangelou, E., & Ioannidis, J. P. A. (2013). Meta-analysis methods for genome-wide association studies and beyond. *Nature Reviews. Genetics*, *14*(6), 379–389. https://doi.org/10.1038/nrg3472

Falagas, M. E., Pitsouni, E. I., Malietzis, G. A., & Pappas, G. (2008). Comparison of PubMed, Scopus, Web of Science, and Google Scholar: Strengths and weaknesses. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *22*(2), 338–342. https://doi.org/10.1096/fj.07-9492LSF

Fang, S. X., Chen, C., Guo, Q., Ke, X. X., Lu, H. L., & Xu, G. (2020). High lncSNHG15 expression may predict poor cancer prognosis: A meta-analysis based on the PRISMA and the bio-informatics analysis. *Bioscience Reports*, *40*(7), BSR20194468. https://doi.org/10.1042/BSR20194468

Fiorini, N., Lipman, D. J., & Lu, Z. (2017). Towards PubMed 2.0. *eLife*, *6*, e28801. https://doi.org/10.7554/eLife.28801

Forero, D. A., Lopez-Leon, S., González-Giraldo, Y., & Bagos, P. G. (2019). Ten simple rules for carrying out and writing meta-analyses. *PLoS Computational Biology*, *15*(5), e1006922. https://doi.org/10.1371/journal.pcbi.1006922

Fountzilas, E., Vo, H. H., Mueller, P., Kurzrock, R., & Tsimberidou, A.-M. (2023). Correlation between biomarkers and treatment outcomes in diverse cancers: A systematic review and meta-analysis of phase I and II immunotherapy clinical trials. *European Journal of Cancer (Oxford, England: 1990)*, *189*, 112927. https://doi.org/10.1016/j.ejca.2023.05.015

Fuchs, E., & Weber, K. (1994). Intermediate filaments: Structure, dynamics, function, and disease. *Annual Review of Biochemistry*, *63*, 345–382. https://doi.org/10.1146/annurev.bi.63.070194.002021

Fuyuhiro, Y., Yashiro, M., Noda, S., Kashiwagi, S., Matsuoka, J., Doi, Y., Kato, Y., Kubo, N., Ohira, M., & Hirakawa, K. (2010). Clinical significance of vimentin-positive gastric cancer cells. *Anticancer Research*, *30*(12), 5239–5243.

Gan, Z., Ding, L., Burckhardt, C. J., Lowery, J., Zaritsky, A., Sitterley, K., Mota, A., Costigliola, N., Starker, C. G., Voytas, D. F., Tytell, J., Goldman, R. D., & Danuser, G. (2016). Vimentin Intermediate Filaments Template Microtubule Networks to Enhance Persistence in Cell Polarity and Directed Migration. *Cell Systems*, *3*(3), 252-263.e8. https://doi.org/10.1016/j.cels.2016.08.007

Gao, Z.-H., Lu, C., Wang, Z.-N., Song, Y.-X., Zhu, J.-L., Gao, P., Sun, J.-X., Chen, X.-W., Wang, M.-X., Dong, Y.-L., & Xu, H.-M. (2014). ILEI: A novel marker for epithelial-mesenchymal transition and poor prognosis in colorectal cancer. *Histopathology*, *65*(4), 527–538. https://doi.org/10.1111/his.12435

Georgakopoulos-Soares, I., Chartoumpekis, D. V., Kyriazopoulou, V., & Zaravinos, A. (2020). EMT Factors and Metabolic Pathways in Cancer. *Frontiers in Oncology*, *10*, 499. https://doi.org/10.3389/fonc.2020.00499

Gilles, C., Polette, M., Mestdagt, M., Nawrocki-Raby, B., Ruggeri, P., Birembaut, P., & Foidart, J.-M. (2003). Transactivation of vimentin by beta-catenin in human breast cancer cells. *Cancer Research*, *63*(10), 2658–2664.

Giró-Perafita, A., Sarrats, A., Pérez-Bueno, F., Oliveras, G., Buxó, M., Brunet, J., Viñas, G., & Miquel, T. P. (2017). Fatty acid synthase expression and its association with clinico-histopathological features in triple-negative breast cancer. *Oncotarget*, *8*(43), 74391–74405. https://doi.org/10.18632/oncotarget.20152

Goldie, K. N., Wedig, T., Mitra, A. K., Aebi, U., Herrmann, H., & Hoenger, A. (2007). Dissecting the 3-D structure of vimentin intermediate filaments by cryo-electron tomography. *Journal of Structural Biology*, *158*(3), 378–385. https://doi.org/10.1016/j.jsb.2006.12.007

Gong, J., Wang, Y., Jiang, B., Xu, B., & Hu, C. (2019). Impact of high-mobility-group A2 overexpression on epithelial-mesenchymal transition in pancreatic cancer. *Cancer Management and Research*, *11*, 4075–4084. https://doi.org/10.2147/CMAR.S199289

Gonzalez, D. M., & Medici, D. (2014). Signaling mechanisms of the epithelial-mesenchymal transition. *Science Signaling*, *7*(344), re8. https://doi.org/10.1126/scisignal.2005189

Goto, Y., Kawano, S., Matsubara, R., Kiyosue, T., Hirano, M., Jinno, T., Maruse, Y., Toyoshima, T., Kitamura, R., Tanaka, H., Oobu, K., & Nakamura, S. (2014). Possible involvement of ΔNp63 downregulation in the invasion and metastasis of oral squamous cell carcinoma via induction of a mesenchymal phenotype. *Clinical & Experimental Metastasis*, *31*(3), 293–306. https://doi.org/10.1007/s10585-013-9628-z

Greco, T., Zangrillo, A., Biondi-Zoccai, G., & Landoni, G. (2013). Meta-analysis: Pitfalls and hints. *Heart, Lung and Vessels*, *5*(4), 219–225.

Gu, M. J., & Choi, J. H. (2014). Epithelial-mesenchymal transition phenotypes are associated with patient survival in intrahepatic cholangiocarcinoma. *Journal of Clinical Pathology*, *67*(3), 229–234. https://doi.org/10.1136/jclinpath-2013-201806

Handra-Luca, A., Hong, S.-M., Walter, K., Wolfgang, C., Hruban, R., & Goggins, M. (2011). Tumour epithelial vimentin expression and outcome of pancreatic ductal adenocarcinomas. *British Journal of Cancer*, *104*(8), 1296–1302. https://doi.org/10.1038/bjc.2011.93

Hao, D., Phan, T., Jagdis, A., Siever, J. E., Klimowicz, A. C., Laskin, J. J., Thomson, T. A., Rose, M. S., Petrillo, S. K., Magliocco, A. M., & Lau, H. Y. (2014). Evaluation of E-cadherin, β-catenin and vimentin protein expression using quantitative immunohistochemistry in nasopharyngeal carcinoma patients. *Clinical and Investigative Medicine. Medecine Clinique Et Experimentale*, *37*(5), E320-330. https://doi.org/10.25011/cim.v37i5.22012

Henderson, P., Wilson, D. C., Satsangi, J., & Stevens, C. (2012). A role for vimentin in Crohn disease. *Autophagy*, *8*(11), 1695–1696. https://doi.org/10.4161/auto.21690

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, *21*(11), 1539–1558. https://doi.org/10.1002/sim.1186

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)*, *327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Hopewel, S., Clarke, M., Moher, D., Wager, E., Middleton, P., Altman, D. G., Schulz, K. F., & The, C. G. (2008). [CONSORT for reporting randomized controlled trials in journal and conference abstracts: Explanation and elaboration]. *Zhong Xi Yi Jie He Xue Bao = Journal of Chinese Integrative Medicine*, *6*(3), 221–232. https://doi.org/10.3736/jcim20080301

Hu, Y., He, M.-Y., Zhu, L.-F., Yang, C.-C., Zhou, M.-L., Wang, Q., Zhang, W., Zheng, Y.-Y., Wang, D.-M., Xu, Z.-Q., Wu, Y.-N., & Liu, L.-K. (2016). Tumor-associated macrophages correlate with the clinicopathological features and poor outcomes via inducing epithelial to mesenchymal transition in oral squamous cell carcinoma. *Journal of Experimental & Clinical Cancer Research: CR*, *35*, 12. https://doi.org/10.1186/s13046-015-0281-z

Huang, R. Y.-J., Guilford, P., & Thiery, J. P. (2012). Early events in cell adhesion and polarity during epithelial-mesenchymal transition. *Journal of Cell Science*, *125*(Pt 19), 4417–4422. https://doi.org/10.1242/jcs.099697

Huang, X.-Y., Zhang, C., Cai, J.-B., Shi, G.-M., Ke, A.-W., Dong, Z.-R., Zhang, P.-F., Fan, J., Peng, B.-G., & Zhou, J. (2014). Comprehensive multiple molecular profile of epithelial mesenchymal transition in intrahepatic cholangiocarcinoma patients. *PloS One*, *9*(5), e96860. https://doi.org/10.1371/journal.pone.0096860

Huang, Z., Ai, Z., Li, N., Xi, H., Gao, X., Wang, F., Tan, X., & Liu, H. (2016). Over expression of galectin-3 associates with short-term poor prognosis in stage II colon cancer. *Cancer Biomarkers: Section A of Disease Markers*, *17*(4), 445–455. https://doi.org/10.3233/CBM-160661

Hugo, H., Ackland, M. L., Blick, T., Lawrence, M. G., Clements, J. A., Williams, E. D., & Thompson, E. W. (2007). Epithelial—Mesenchymal and mesenchymal—Epithelial transitions in carcinoma progression. *Journal of Cellular Physiology*, *213*(2), 374–383. https://doi.org/10.1002/jcp.21223

Imai, D., Yoshizumi, T., Okano, S., Itoh, S., Ikegami, T., Harada, N., Aishima, S., Oda, Y., & Maehara, Y. (2019). IFN-γ Promotes Epithelial-Mesenchymal Transition and the Expression of PD-L1 in Pancreatic Cancer. *The Journal of Surgical Research*, *240*, 115–123. https://doi.org/10.1016/j.jss.2019.02.038

Imajyo, I., Sugiura, T., Kobayashi, Y., Shimoda, M., Ishii, K., Akimoto, N., Yoshihama, N., Kobayashi, I., & Mori, Y. (2012). T-box transcription factor Brachyury expression is correlated with epithelial-mesenchymal transition and lymph node metastasis in oral squamous cell carcinoma. *International Journal of Oncology*, *41*(6), 1985–1995. https://doi.org/10.3892/ijo.2012.1673

Ingels, A., Hew, M., Algaba, F., de Boer, O. J., van Moorselaar, R. J. A., Horenblas, S., Zondervan, P., de la Rosette, J. J. M. C. H., & Pilar Laguna Pes, M. (2017). Vimentin over-expression and carbonic anhydrase IX under-expression are independent predictors of recurrence, specific and overall survival in non-metastatic clear-cell renal carcinoma: A validation study. *World Journal of Urology*, *35*(1), 81–87. https://doi.org/10.1007/s00345-016-1854-y

J, C., T, W., Yc, Z., F, G., Zh, Z., H, X., Sl, W., & Lz, S. (2014). Aquaporin 3 promotes epithelial-mesenchymal transition in gastric cancer. *Journal of Experimental & Clinical Cancer Research : CR*, *33*(1). https://doi.org/10.1186/1756-9966-33-38

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*, *17*(1), 1–12. https://doi.org/10.1016/0197-2456(95)00134-4

Jin, Z., Zhou, X., & He, J. (2015). Statistical methods for dealing with publication bias in meta-analysis. *Statistics in Medicine*, *34*(2), 343–360. https://doi.org/10.1002/sim.6342

Jiu, Y., Peränen, J., Schaible, N., Cheng, F., Eriksson, J. E., Krishnan, R., & Lappalainen, P. (2017). Vimentin intermediate filaments control actin stress fiber assembly through GEF-H1 and RhoA. *Journal of Cell Science*, *130*(5), 892–902. https://doi.org/10.1242/jcs.196881

Kahlert, U. D., Joseph, J. V., & Kruyt, F. A. E. (2017). EMT- and MET-related processes in nonepithelial tumors: Importance for disease progression, prognosis, and therapeutic opportunities. *Molecular Oncology*, *11*(7), 860–877. https://doi.org/10.1002/1878-0261.12085

Kalluri, R., & Weinberg, R. A. (2009). The basics of epithelial-mesenchymal transition. *The Journal of Clinical Investigation*, *119*(6), 1420–1428. https://doi.org/10.1172/JCI39104

Karamagkiolas, S., Giotakis, I., Kyrodimos, E., Giotakis, E. I., Kataki, A., Karagianni, F., & Lazaris, A. M. (2019). Expression of vimentin (VIM) and metastasis-associated 1 (MTA1) protein in laryngeal squamous cell carcinoma are associated with prognostic outcome of patients. *American Journal of Otolaryngology*, *40*(4), 487–493. https://doi.org/10.1016/j.amjoto.2019.04.002

Kato, K., Shimasaki, M., Kato, T., Segami, N., & Ueda, Y. (2018). Expression of Sphingosine Kinase-1 Is Associated with Invasiveness and Poor Prognosis of Oral Squamous Cell Carcinoma. *Anticancer Research*, *38*(3), 1361–1368. https://doi.org/10.21873/anticanres.12359

Ke, B., Guo, X.-F., Li, N., Wu, L.-L., Li, B., Zhang, R.-P., & Liang, H. (2019). Clinical significance of Stathmin1 expression and epithelial-mesenchymal transition in curatively resected gastric cancer. *Molecular and Clinical Oncology*, *10*(2), 214–222. https://doi.org/10.3892/mco.2018.1774

Kidd, M. E., Shumaker, D. K., & Ridge, K. M. (2014). The role of vimentin intermediate filaments in the progression of lung cancer. *American Journal of Respiratory Cell and Molecular Biology*, *50*(1), 1–6. https://doi.org/10.1165/rcmb.2013-0314TR

Kim, A., Bae, Y. K., Gu, M. J., Kim, J. Y., Jang, K. Y., Bae, H.-I., Lee, H. J., & Hong, S.-M. (2013). Epithelial-mesenchymal transition phenotype is associated with patient survival in small intestinal adenocarcinoma. *Pathology*, *45*(6), 567–573. https://doi.org/10.1097/PAT.0b013e3283650bab

Kim, H. L., Seligson, D., Liu, X., Janzen, N., Bui, M. H. T., Yu, H., Shi, T., Figlin, R. A., Horvath, S., & Belldegrun, A. S. (2004). Using protein expressions to predict survival in clear cell renal carcinoma. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *10*(16), 5464–5471. https://doi.org/10.1158/1078-0432.CCR-04-0488

Kim, H.-Y. (2017). Statistical notes for clinical researchers: Risk difference, risk ratio, and odds ratio. *Restorative Dentistry & Endodontics*, *42*(1), 72–76. https://doi.org/10.5395/rde.2017.42.1.72

Kim, M. A., Lee, H. S., Lee, H. E., Kim, J. H., Yang, H.-K., & Kim, W. H. (2009). Prognostic importance of epithelial-mesenchymal transition-related protein expression in gastric carcinoma. *Histopathology*, *54*(4), 442–451. https://doi.org/10.1111/j.1365-2559.2009.03247.x

Kong, F.-F., Qu, Z.-Q., Yuan, H.-H., Wang, J.-Y., Zhao, M., Guo, Y.-H., Shi, J., Gong, X.-D., Zhu, Y.-L., Liu, F., Zhang, W.-Y., & Jiang, B. (2014). Overexpression of FOXM1 is associated with EMT and is a predictor of poor prognosis in non-small cell lung cancer. *Oncology Reports*, *31*(6), 2660–2668. https://doi.org/10.3892/or.2014.3129

Lewis, S., & Clarke, M. (2001). Forest plots: Trying to see the wood and the trees. *BMJ (Clinical Research Ed.)*, *322*(7300), 1479–1480. https://doi.org/10.1136/bmj.322.7300.1479

Li, C., & Ma, Y.-Q. (2022). Prognostic significance of sex determining region Y-box 2, E-cadherin, and vimentin in esophageal squamous cell carcinoma. *World Journal of Clinical Cases*, *10*(27), 9657–9669. https://doi.org/10.12998/wjcc.v10.i27.9657

Li, D., Fan, S., Yu, F., Zhu, X., Song, Y., Ye, M., Fan, L., & Lv, Z. (2018). FOXD1 Promotes Cell Growth and Metastasis by Activation of Vimentin in NSCLC. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*, *51*(6), 2716–2731. https://doi.org/10.1159/000495962

Li, J., Liu, Y., Xue, J., Xu, M., Zhang, J., Liu, J., & Wang, W. (2019). Krüppel-Like Factor 8 Overexpression Correlates with Poor Prognosis in Non-Small Cell Lung Cancer. *Pathology Oncology Research: POR*, *25*(1), 115–121. https://doi.org/10.1007/s12253-017-0321-4

Lien, H. C., Hsiao, Y. H., Lin, Y. S., Yao, Y. T., Juan, H. F., Kuo, W. H., Hung, M.-C., Chang, K. J., & Hsieh, F. J. (2007). Molecular signatures of metaplastic carcinoma of the breast by large-scale transcriptional profiling: Identification of genes potentially related to epithelial-mesenchymal transition. *Oncogene*, *26*(57), 7859–7871. https://doi.org/10.1038/sj.onc.1210593

Lilienbaum, A., & Paulin, D. (1993). Activation of the human vimentin gene by the Tax human T-cell leukemia virus. I. Mechanisms of regulation by the NF-kappa B transcription factor. *The Journal of Biological Chemistry*, *268*(3), 2180–2188.

Lin, H., Huang, B., Wang, H., Liu, X., Hong, Y., Qiu, S., & Zheng, J. (2018). MTHFD2 Overexpression Predicts Poor Prognosis in Renal Cell Carcinoma and is Associated with Cell Proliferation and Vimentin-Modulated Migration and Invasion. *Cellular Physiology and Biochemistry: International Journal of*

Experimental Cellular Physiology, Biochemistry, and Pharmacology, *51*(2), 991–1000. https://doi.org/10.1159/000495402

Lin, J., Lu, J., Wang, C., & Xue, X. (2017). The prognostic values of the expression of Vimentin, TP53, and Podoplanin in patients with cervical cancer. *Cancer Cell International*, *17*, 80. https://doi.org/10.1186/s12935-017-0450-6

Lin, L., & Chu, H. (2018). Quantifying publication bias in meta-analysis. *Biometrics*, *74*(3), 785–794. https://doi.org/10.1111/biom.12817

Lin, Y.-T., & Wu, K.-J. (2020). Epigenetic regulation of epithelial-mesenchymal transition: Focusing on hypoxia and TGF-β signaling. *Journal of Biomedical Science*, *27*(1), 39. https://doi.org/10.1186/s12929-020-00632-3

Liu, B., Miyake, H., Nishikawa, M., & Fujisawa, M. (2015). Expression profile of epithelial-mesenchymal transition markers in non-muscle-invasive urothelial carcinoma of the bladder: Correlation with intravesical recurrence following transurethral resection. *Urologic Oncology*, *33*(3), 110.e11-18. https://doi.org/10.1016/j.urolonc.2014.08.012

Liu, L., Wu, N., Wang, Y., Zhang, X., Xia, B., Tang, J., Cai, J., Zhao, Z., Liao, Q., & Wang, J. (2019). TRPM7 promotes the epithelial-mesenchymal transition in ovarian cancer through the calcium-related PI3K / AKT oncogenic signaling. *Journal of Experimental & Clinical Cancer Research: CR*, *38*(1), 106. https://doi.org/10.1186/s13046-019-1061-y

Liu, L.-G., Yan, X.-B., Xie, R.-T., Jin, Z.-M., & Yang, Y. (2017). Stromal Expression of Vimentin Predicts the Clinical Outcome of Stage II Colorectal Cancer for High-Risk Patients. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *23*, 2897–2905. https://doi.org/10.12659/msm.904486

Liu, L.-K., Jiang, X.-Y., Zhou, X.-X., Wang, D.-M., Song, X.-L., & Jiang, H.-B. (2010). Upregulation of vimentin and aberrant expression of E-cadherin/beta-catenin complex in oral squamous cell carcinomas: Correlation with the clinicopathological features and patient outcome. *Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc*, *23*(2), 213–224. https://doi.org/10.1038/modpathol.2009.160

Liu, P.-F., Kang, B.-H., Wu, Y.-M., Sun, J.-H., Yen, L.-M., Fu, T.-Y., Lin, Y.-C., Liou, H.-H., Lin, Y.-S., Sie, H.-C., Hsieh, I.-C., Tseng, Y.-K., Shu, C.-W., Hsieh, Y.-D., &

Ger, L.-P. (2017). Vimentin is a potential prognostic factor for tongue squamous cell carcinoma among five epithelial-mesenchymal transition-related proteins. *PloS One*, *12*(6), e0178581. https://doi.org/10.1371/journal.pone.0178581

Liu, S., Huang, J., Zhang, Y., Liu, Y., Zuo, S., & Li, R. (2019). MAP2K4 interacts with Vimentin to activate the PI3K/AKT pathway and promotes breast cancer pathogenesis. *Aging*, *11*(22), 10697–10710. https://doi.org/10.18632/aging.102485

Liu, S., Liu, L., Ye, W., Ye, D., Wang, T., Guo, W., Liao, Y., Xu, D., Song, H., Zhang, L., Zhu, H., Deng, J., & Zhang, Z. (2016). High Vimentin Expression Associated with Lymph Node Metastasis and Predicated a Poor Prognosis in Oral Squamous Cell Carcinoma. *Scientific Reports*, *6*, 38834. https://doi.org/10.1038/srep38834

Liu, T., Zhang, X., Shang, M., Zhang, Y., Xia, B., Niu, M., Liu, Y., & Pang, D. (2013). Dysregulated expression of Slug, vimentin, and E-cadherin correlates with poor clinical outcome in patients with basal-like breast cancer. *Journal of Surgical Oncology*, *107*(2), 188–194. https://doi.org/10.1002/jso.23240

Liu, W.-F., Ji, S.-R., Sun, J.-J., Zhang, Y., Liu, Z.-Y., Liang, A.-B., & Zeng, H.-Z. (2012). CD146 expression correlates with epithelial-mesenchymal transition markers and a poor prognosis in gastric cancer. *International Journal of Molecular Sciences*, *13*(5), 6399–6406. https://doi.org/10.3390/ijms13056399

Liu, Y., Zhou, Y.-D., Xiao, Y.-L., Li, M.-H., Wang, Y., Kan, X., Li, Q.-Y., Lu, J.-G., & Jin, D.-J. (2015). Cyr61/CCN1 overexpression induces epithelial-mesenchymal transition leading to laryngeal tumor invasion and metastasis and poor prognosis. *Asian Pacific Journal of Cancer Prevention: APJCP*, *16*(7), 2659–2664. https://doi.org/10.7314/apjcp.2015.16.7.2659

Liu, Z., Zhang, Y., Niu, Y., Li, K., Liu, X., Chen, H., & Gao, C. (2014). A systematic review and meta-analysis of diagnostic and prognostic serum biomarkers of colorectal cancer. *PloS One*, *9*(8), e103910. https://doi.org/10.1371/journal.pone.0103910

Lobo, J., Monteiro-Reis, S., Guimarães-Teixeira, C., Lopes, P., Carneiro, I., Jerónimo, C., & Henrique, R. (2020). Practicability of clinical application of bladder cancer molecular classification and additional value of epithelial-to-mesenchymal transition: Prognostic value of vimentin expression. *Journal of Translational Medicine*, *18*(1), 303. https://doi.org/10.1186/s12967-020-02475-w

Lu, W., Luo, J.-Y., Wu, M.-H., Hou, J.-Y., Yang, X., Chen, G., & Feng, Z.-B. (2019). Expression of vimentin in nasopharyngeal carcinoma and its possible molecular mechanism: A study based on immunohistochemistry and bioinformatics analysis. *Pathology, Research and Practice*, *215*(5), 1020–1032. https://doi.org/10.1016/j.prp.2019.02.010

Luo, W., Fang, W., Li, S., & Yao, K. (2012). Aberrant expression of nuclear vimentin and related epithelial-mesenchymal transition markers in nasopharyngeal carcinoma. *International Journal of Cancer*, *131*(8), 1863–1873. https://doi.org/10.1002/ijc.27467

Maehira, H., Miyake, T., Iida, H., Tokuda, A., Mori, H., Yasukawa, D., Mukaisho, K.-I., Shimizu, T., & Tani, M. (2019). Vimentin Expression in Tumor Microenvironment Predicts Survival in Pancreatic Ductal Adenocarcinoma: Heterogeneity in Fibroblast Population. *Annals of Surgical Oncology*, *26*(13), 4791–4804. https://doi.org/10.1245/s10434-019-07891-x

Mao, X., Chen, D., Wu, J., Li, J., Zhou, H., Wu, Y., & Duan, X. (2013). Differential expression of fascin, E-cadherin and vimentin: Proteins associated with survival of cholangiocarcinoma patients. *The American Journal of the Medical Sciences*, *346*(4), 261–268. https://doi.org/10.1097/MAJ.0b013e3182707108

Mathew, J. L. (2022). Systematic Reviews and Meta-Analysis: A Guide for Beginners. *Indian Pediatrics*, *59*(4), 320–330. https://doi.org/10.1007/s13312-022-2500-y

McConkey, D. J., Choi, W., Marquis, L., Martin, F., Williams, M. B., Shah, J., Svatek, R., Das, A., Adam, L., Kamat, A., Siefker-Radtke, A., & Dinney, C. (2009). Role of epithelial-to-mesenchymal transition (EMT) in drug sensitivity and metastasis in bladder cancer. *Cancer and Metastasis Reviews*, *28*(3–4), 335–344. https://doi.org/10.1007/s10555-009-9194-7

McKeon, F. D., Kirschner, M. W., & Caput, D. (1986). Homologies in both primary and secondary structure between nuclear envelope and intermediate filament proteins. *Nature*, *319*(6053), 463–468. https://doi.org/10.1038/319463a0

Mendez, M. G., Kojima, S.-I., & Goldman, R. D. (2010). Vimentin induces changes in cell shape, motility, and adhesion during the epithelial to mesenchymal transition. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *24*(6), 1838–1851. https://doi.org/10.1096/fj.09-151639

Moch, H., Schraml, P., Bubendorf, L., Mirlacher, M., Kononen, J., Gasser, T., Mihatsch, M. J., Kallioniemi, O. P., & Sauter, G. (1999). High-throughput tissue microarray analysis to evaluate genes uncovered by cDNA microarray screening in renal cell carcinoma. *The American Journal of Pathology*, *154*(4), 981–986. https://doi.org/10.1016/S0002-9440(10)65349-7

Moskalewicz, A., & Oremus, M. (2020). No clear choice between Newcastle-Ottawa Scale and Appraisal Tool for Cross-Sectional Studies to assess methodological quality in cross-sectional studies of health-related quality of life and breast cancer. *Journal of Clinical Epidemiology*, *120*, 94–103. https://doi.org/10.1016/j.jclinepi.2019.12.013

Nakamura, E. T., Park, A., Pereira, M. A., Kikawa, D., & Tustumi, F. (2024). Prognosis value of heat-shock proteins in esophageal and esophagogastric cancer: A systematic review and meta-analysis. *World Journal of Gastrointestinal Oncology*, *16*(4), 1578–1595. https://doi.org/10.4251/wjgo.v16.i4.1578

Nakashima, H., Jiang, S.-X., Sato, Y., Hoshi, K., Matsumoto, T., Nagashio, R., Kobayashi, M., Matsuo, Y., Shiomi, K., Hayakawa, K., Saegusa, M., & Satoh, Y. (2015). Prevalent and up-regulated vimentin expression in micropapillary components of lung adenocarcinomas and its adverse prognostic significance. *Pathology International*, *65*(4), 183–192. https://doi.org/10.1111/pin.12257

Nakashima, Y., Yoshinaga, K., Kitao, H., Ando, K., Kimura, Y., Saeki, H., Oki, E., Morita, M., Kakeji, Y., Hirahashi, M., Oda, Y., & Maehara, Y. (2013). Podoplanin is expressed at the invasive front of esophageal squamous cell carcinomas and is involved in collective cell invasion. *Cancer Science*, *104*(12), 1718–1725. https://doi.org/10.1111/cas.12286

Nassour, A.-J., Jain, A., Hui, N., Siopis, G., Symons, J., & Woo, H. (2023). Relative Risk of Bladder and Kidney Cancer in Lynch Syndrome: Systematic Review and Meta-Analysis. *Cancers*, *15*(2), 506. https://doi.org/10.3390/cancers15020506

NCBI Resource Coordinators. (2016). Database resources of the National Center for Biotechnology Information. *Nucleic Acids Research*, *44*(D1), D7-19. https://doi.org/10.1093/nar/gkv1290

Ngan, C. Y., Yamamoto, H., Seshimo, I., Tsujino, T., Man-i, M., Ikeda, J.-I., Konishi, K., Takemasa, I., Ikeda, M., Sekimoto, M., Matsuura, N., & Monden, M. (2007). Quantitative evaluation of vimentin expression in tumour stroma of colorectal

cancer. *British Journal of Cancer*, *96*(6), 986–992. https://doi.org/10.1038/sj.bjc.6603651

Ni, W.-D., Yang, Z.-T., Cui, C.-A., Cui, Y., Fang, L.-Y., & Xuan, Y.-H. (2017). Tenascin-C is a potential cancer-associated fibroblasts marker and predicts poor prognosis in prostate cancer. *Biochemical and Biophysical Research Communications*, *486*(3), 607–612. https://doi.org/10.1016/j.bbrc.2017.03.021

Nikolopoulos, G. K., Bagos, P. G., & Bonovas, S. (2011). Developing the evidence base for cancer chemoprevention: Use of meta-analysis. *Current Drug Targets*, *12*(13), 1989–1997. https://doi.org/10.2174/138945011798184191

Otsuki, S., Inokuchi, M., Enjoji, M., Ishikawa, T., Takagi, Y., Kato, K., Yamada, H., Kojima, K., & Sugihara, K. (2011). Vimentin expression is associated with decreased survival in gastric cancer. *Oncology Reports*, *25*(5), 1235–1242. https://doi.org/10.3892/or.2011.1185

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, *372*, n71. https://doi.org/10.1136/bmj.n71

Papakostidis, C., & Giannoudis, P. V. (2023). Meta-analysis. What have we learned? *Injury*, *54 Suppl 3*, S30–S34. https://doi.org/10.1016/j.injury.2022.06.012

Patel, N. A., Patel, P. S., & Vora, H. H. (2015). 33782057. *Breast Disease*, *35*(2), 113–127. https://doi.org/10.3233/BD-140395

Pattabiraman, S., Azad, G. K., Amen, T., Brielle, S., Park, J. E., Sze, S. K., Meshorer, E., & Kaganovich, D. (2020). Vimentin protects differentiating stem cells from stress. *Scientific Reports*, *10*(1), 19525. https://doi.org/10.1038/s41598-020-76076-4

Patteson, A. E., Vahabikashi, A., Pogoda, K., Adam, S. A., Mandal, K., Kittisopikul, M., Sivagurunathan, S., Goldman, A., Goldman, R. D., & Janmey, P. A. (2019). Vimentin protects cells against nuclear rupture and DNA damage during migration. *The Journal of Cell Biology*, *218*(12), 4079–4092. https://doi.org/10.1083/jcb.201902046

Perlson, E., Michaelevski, I., Kowalsman, N., Ben-Yaakov, K., Shaked, M., Seger, R., Eisenstein, M., & Fainzilber, M. (2006). Vimentin Binding to Phosphorylated Erk Sterically Hinders Enzymatic Dephosphorylation of the Kinase. *Journal of Molecular Biology*, *364*(5), 938–944. https://doi.org/10.1016/j.jmb.2006.09.056

Qin, Y., Yu, J., Zhang, M., Qin, F., & Lan, X. (2019). ZEB1 promotes tumorigenesis and metastasis in hepatocellular carcinoma by regulating the expression of vimentin. *Molecular Medicine Reports*, *19*(3), 2297–2306. https://doi.org/10.3892/mmr.2019.9866

Ranganathan, P., Aggarwal, R., & Pramesh, C. S. (2015). Common pitfalls in statistical analysis: Odds versus risk. *Perspectives in Clinical Research*, *6*(4), 222–224. https://doi.org/10.4103/2229-3485.167092

Richardson, F., Young, G. D., Sennello, R., Wolf, J., Argast, G. M., Mercado, P., Davies, A., Epstein, D. M., & Wacker, B. (2012). The evaluation of E-Cadherin and vimentin as biomarkers of clinical outcomes among patients with non-small cell lung cancer treated with erlotinib as second- or third-line therapy. *Anticancer Research*, *32*(2), 537–552.

Richardson, M., Garner, P., & Donegan, S. (2019). Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clinical Epidemiology and Global Health*, *7*(2), 192–198. https://doi.org/10.1016/j.cegh.2018.05.005

Rittling, S. R., & Baserga, R. (1987). Functional analysis and growth factor regulation of the human vimentin promoter. *Molecular and Cellular Biology*, *7*(11), 3908–3915. https://doi.org/10.1128/mcb.7.11.3908-3915.1987

Rittling, S. R., Coutinho, L., Amram, T., & Kolbe, M. (1989). AP-1/jun binding sites mediate serum inducibility of the human vimentin promoter. *Nucleic Acids Research*, *17*(4), 1619–1633. https://doi.org/10.1093/nar/17.4.1619

Roberts, M. R., Ashrafzadeh, S., & Asgari, M. M. (2019). Research Techniques Made Simple: Interpreting Measures of Association in Clinical Research. *Journal of Investigative Dermatology*, *139*(3), 502-511.e1. https://doi.org/10.1016/j.jid.2018.12.023

Roche, J. (2018). The Epithelial-to-Mesenchymal Transition in Cancer. *Cancers*, *10*(2), 52. https://doi.org/10.3390/cancers10020052

Rodríguez-Pinilla, S. M., Sarrió, D., Honrado, E., Moreno-Bueno, G., Hardisson, D., Calero, F., Benítez, J., & Palacios, J. (2007). Vimentin and laminin expression is associated with basal-like phenotype in both sporadic and BRCA1-associated breast carcinomas. *Journal of Clinical Pathology*, *60*(9), 1006–1012. https://doi.org/10.1136/jcp.2006.042143

Russo, M. W. (2007). How to Review a Meta-analysis. *Gastroenterology & Hepatology*, *3*(8), 637–642.

Sabo, E., Miselevich, I., Bejar, J., Segenreich, M., Wald, M., Moskovitz, B., & Nativ, O. (1997). 25547164. *British Journal of Urology*, *80*(6), 864–868. https://doi.org/10.1046/j.1464-410x.1997.00489.x

Sagoo, G. S., Little, J., & Higgins, J. P. T. (2009). Systematic reviews of genetic association studies. Human Genome Epidemiology Network. *PLoS Medicine*, *6*(3), e28. https://doi.org/10.1371/journal.pmed.1000028

Santos, M. I., Tuzlakoglu, K., Fuchs, S., Gomes, M. E., Peters, K., Unger, R. E., Piskin, E., Reis, R. L., & Kirkpatrick, C. J. (2008). Endothelial cell colonization and angiogenic potential of combined nano- and micro-fibrous scaffolds for bone tissue engineering. *Biomaterials*, *29*(32), 4306–4313. https://doi.org/10.1016/j.biomaterials.2008.07.033

Sas-Korczynska, B., Niemiec, J., Harazin-Lechowska, A., Korzeniowski, S., Martynow, D., Adamczyk, A., & Sokolowski, A. (2014). The biological markers and results of treatment in male breast cancer patients. The Cracow experience. *Neoplasma*, *61*(3), 331–339. https://doi.org/10.4149/neo_2014_043

Satelli, A., & Li, S. (2011). Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cellular and Molecular Life Sciences: CMLS*, *68*(18), 3033–3046. https://doi.org/10.1007/s00018-011-0735-1

Sato, N., Fujishima, F., Nakamura, Y., Aoyama, Y., Onodera, Y., Ozawa, Y., Ito, K., Ishida, H., Kamei, T., Watanabe, M., & Sasano, H. (2018). Myosin 5a regulates tumor migration and epithelial-mesenchymal transition in esophageal squamous cell carcinoma: Utility as a prognostic factor. *Human Pathology*, *80*, 113–122. https://doi.org/10.1016/j.humpath.2018.06.002

Sawant, S. S., Vaidya, M. m, Chaukar, D. A., Alam, H., Dmello, C., Gangadaran, P., Kannan, S., Kane, S., Dange, P. P., Dey, N., Ranganathan, K., & D'Cruz, A. K. (2014). Clinical significance of aberrant vimentin expression in oral

premalignant lesions and carcinomas. *Oral Diseases*, *20*(5), 453–465. https://doi.org/10.1111/odi.12151

Scanlon, C. S., Van Tubergen, E. A., Inglehart, R. C., & D'Silva, N. J. (2013). Biomarkers of epithelial-mesenchymal transition in squamous cell carcinoma. *Journal of Dental Research*, *92*(2), 114–121. https://doi.org/10.1177/0022034512467352

Schoumacher, M., Goldman, R. D., Louvard, D., & Vignjevic, D. M. (2010). Actin, microtubules, and vimentin intermediate filaments cooperate for elongation of invadopodia. *Journal of Cell Biology*, *189*(3), 541–556. https://doi.org/10.1083/jcb.200909113

Sedgwick, P. (2015a). Meta-analyses: What is heterogeneity? *BMJ (Clinical Research Ed.)*, *350*, h1435. https://doi.org/10.1136/bmj.h1435

Sedgwick, P. (2015b). What is publication bias in a meta-analysis? *BMJ*, h4419. https://doi.org/10.1136/bmj.h4419

Sella, A., Logothetis, C. J., Ro, J. Y., Swanson, D. A., & Samuels, M. L. (1987). Sarcomatoid renal cell carcinoma. A treatable entity. *Cancer*, *60*(6), 1313–1318. https://doi.org/10.1002/1097-0142(19870915)60:6<1313::AID-CNCR2820600625>3.0.CO;2-1

Shabbir, S. H., Cleland, M. M., Goldman, R. D., & Mrksich, M. (2014). Geometric control of vimentin intermediate filaments. *Biomaterials*, *35*(5), 1359–1366. https://doi.org/10.1016/j.biomaterials.2013.10.008

Shadish, W. R., & Lecy, J. D. (2015). The meta-analytic big bang. *Research Synthesis Methods*, *6*(3), 246–264. https://doi.org/10.1002/jrsm.1132

Shaheen, N., Shaheen, A., Ramadan, A., Hefnawy, M. T., Ramadan, A., Ibrahim, I. A., Hassanein, M. E., Ashour, M. E., & Flouty, O. (2023). Appraising systematic reviews: A comprehensive guide to ensuring validity and reliability. *Frontiers in Research Metrics and Analytics*, *8*, 1268045. https://doi.org/10.3389/frma.2023.1268045

Shi, C., Xu, L., Tang, Z., Zhang, W., Wei, Y., Ni, J., Zhang, S., & Feng, J. (2019). Knockdown of Nemo-like kinase promotes metastasis in non-small-cell lung cancer. *Oncology Reports*, *42*(3), 1090–1100. https://doi.org/10.3892/or.2019.7226

Shi, Z.-G., Li, S.-Q., Li, Z.-J., Zhu, X.-J., Xu, P., & Liu, G. (2015). Expression of vimentin and survivin in clear cell renal cell carcinoma and correlation with p53. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*, *17*(1), 65–73. https://doi.org/10.1007/s12094-014-1199-1

Sistrom, C. L., & Garvan, C. W. (2004). Proportions, Odds, and Risk. *Radiology*, *230*(1), 12–19. https://doi.org/10.1148/radiol.2301031028

Song, H., Ci, H., Xu, J., Xu, Z., Zhang, Y., Wang, Y., Wu, S., & Tao, Y. (2018). Vasculogenic mimicry and expression of slug and vimentin correlate with metastasis and prognosis in non-small cell lung cancer. *International Journal of Clinical and Experimental Pathology*, *11*(5), 2749–2758.

Sowa, T., Menju, T., Sonobe, M., Nakanishi, T., Shikuma, K., Imamura, N., Motoyama, H., Hijiya, K., Aoyama, A., Chen, F., Sato, T., Kobayashi, M., Yoshizawa, A., Haga, H., Sozu, T., & Date, H. (2015). Association between epithelial-mesenchymal transition and cancer stemness and their effect on the prognosis of lung adenocarcinoma. *Cancer Medicine*, *4*(12), 1853–1862. https://doi.org/10.1002/cam4.556

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, *25*(9), 603–605. https://doi.org/10.1007/s10654-010-9491-z

Steinert, P. M. (1993). Structure, function, and dynamics of keratin intermediate filaments. *The Journal of Investigative Dermatology*, *100*(6), 729–734. https://doi.org/10.1111/1523-1747.ep12475665

Steinert, P. M., Marekov, L. N., Fraser, R. D., & Parry, D. A. (1993). Keratin intermediate filament structure. Crosslinking studies yield quantitative information on molecular dimensions and mechanism of assembly. *Journal of Molecular Biology*, *230*(2), 436–452. https://doi.org/10.1006/jmbi.1993.1161

Suprewicz, Ł., Swoger, M., Gupta, S., Piktel, E., Byfield, F. J., Iwamoto, D. V., Germann, D., Reszeć, J., Marcińczyk, N., Carroll, R. J., Lenart, M., Pyrc, K., Janmey, P., Schwarz, J. M., Bucki, R., & Patteson, A. (2021). *Extracellular vimentin as a target against SARS-CoV-2 host cell invasion*. https://doi.org/10.1101/2021.01.08.425793

Szumilas, M. (2010). Explaining odds ratios. *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal De l'Academie Canadienne De Psychiatrie De L'enfant Et De L'adolescent*, *19*(3), 227–229.

Tadokoro, A., Kanaji, N., Liu, D., Yokomise, H., Haba, R., Ishii, T., Takagi, T., Watanabe, N., Kita, N., Kadowaki, N., & Bandoh, S. (2016). Vimentin Regulates Invasiveness and Is a Poor Prognostic Marker in Non-small Cell Lung Cancer. *Anticancer Research*, *36*(4), 1545–1551.

Tanaka, M., Kijima, H., Shimada, H., Makuuchi, H., Ozawa, S., & Inokuchi, S. (2015). Expression of podoplanin and vimentin is correlated with prognosis in esophageal squamous cell carcinoma. *Molecular Medicine Reports*, *12*(3), 4029–4036. https://doi.org/10.3892/mmr.2015.3966

Terashita, K., Chuma, M., Hatanaka, Y., Hatanaka, K., Mitsuhashi, T., Yokoo, H., Ohmura, T., Ishizu, H., Muraoka, S., Nagasaka, A., Tsuji, T., Yamamoto, Y., Kurauchi, N., Shimoyama, N., Toyoda, H., Kumada, T., Kaneoka, Y., Maeda, A., Ogawa, K., … Sakamoto, N. (2016). ZEB1 expression is associated with prognosis of intrahepatic cholangiocarcinoma. *Journal of Clinical Pathology*, *69*(7), 593–599. https://doi.org/10.1136/jclinpath-2015-203115

Tian, W., Wang, G., Yang, J., Pan, Y., & Ma, Y. (2013). Prognostic role of E-cadherin and Vimentin expression in various subtypes of soft tissue leiomyosarcomas. *Medical Oncology (Northwood, London, England)*, *30*(1), 401. https://doi.org/10.1007/s12032-012-0401-y

Tian, Y., Qi, P., Niu, Q., & Hu, X. (2020). Combined Snail and E-cadherin Predicts Overall Survival of Cervical Carcinoma Patients: Comparison Among Various Epithelial-Mesenchymal Transition Proteins. *Frontiers in Molecular Biosciences*, *7*, 22. https://doi.org/10.3389/fmolb.2020.00022

Tibshirani, R. (1982). A plain man's guide to the proportional hazards model. *Clinical and Investigative Medicine. Medecine Clinique Et Experimentale*, *5*(1), 63–68.

Tierney, J. F., Stewart, L. A., Ghersi, D., Burdett, S., & Sydes, M. R. (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, *8*(1), 16. https://doi.org/10.1186/1745-6215-8-16

Toiyama, Y., Yasuda, H., Saigusa, S., Tanaka, K., Inoue, Y., Goel, A., & Kusunoki, M. (2013). Increased expression of Slug and Vimentin as novel predictive

biomarkers for lymph node metastasis and poor prognosis in colorectal cancer. *Carcinogenesis*, *34*(11), 2548–2557. https://doi.org/10.1093/carcin/bgt282

Toy, H. I., Okmen, D., Kontou, P. I., Georgakilas, A. G., & Pavlopoulou, A. (2019). HOTAIR as a Prognostic Predictor for Diverse Human Cancers: A Meta- and Bioinformatics Analysis. *Cancers*, *11*(6), 778. https://doi.org/10.3390/cancers11060778

Tseng, Y.-H., Chang, K.-W., Yang, C.-C., Liu, C.-J., Kao, S.-Y., Liu, T.-Y., & Lin, S.-C. (2012). Association between areca-stimulated vimentin expression and the progression of head and neck cancers. *Head & Neck*, *34*(2), 245–253. https://doi.org/10.1002/hed.21726

Tseng, Y.-H., Yang, C.-C., Lin, S.-C., Cheng, C.-C., Lin, S.-H., Liu, C.-J., & Chang, K.-W. (2011). Areca nut extract upregulates vimentin by activating PI3K/AKT signaling in oral carcinoma. *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, *40*(2), 160–166. https://doi.org/10.1111/j.1600-0714.2010.00978.x

Tsoukalas, N., Aravantinou-Fatorou, E., Tolia, M., Giaginis, C., Galanopoulos, M., Kiakou, M., Kostakis, I. D., Dana, E., Vamvakaris, I., Korogiannos, A., Tsiambas, E., Salemis, N., Kyrgias, G., Karameris, A., & Theocharis, S. (2017). Epithelial-Mesenchymal Transition in Non Small-cell Lung Cancer. *Anticancer Research*, *37*(4), 1773–1778. https://doi.org/10.21873/anticanres.11510

Tsuruta, D., & Jones, J. C. R. (2003). The vimentin cytoskeleton regulates focal contact size and adhesion of endothelial cells subjected to shear stress. *Journal of Cell Science*, *116*(24), 4977–4984. https://doi.org/10.1242/jcs.00823

Tzivion, G., Luo, Z. J., & Avruch, J. (2000). Calyculin A-induced vimentin phosphorylation sequesters 14-3-3 and displaces other 14-3-3 partners in vivo. *The Journal of Biological Chemistry*, *275*(38), 29772–29778. https://doi.org/10.1074/jbc.M001207200

Ueyama, T., Nagai, E., Yao, T., & Tsuneyoshi, M. (1993). Vimentin-positive gastric carcinomas with rhabdoid features. A clinicopathologic and immunohistochemical study. *The American Journal of Surgical Pathology*, *17*(8), 813–819. https://doi.org/10.1097/00000478-199308000-00006

Usman, S., Jamal, A., Teh, M.-T., & Waseem, A. (2020). Major Molecular Signaling Pathways in Oral Cancer Associated With Therapeutic Resistance. *Frontiers in Oral Health*, *1*, 603160. https://doi.org/10.3389/froh.2020.603160

Usman, S., Waseem, N. H., Nguyen, T. K. N., Mohsin, S., Jamal, A., Teh, M.-T., & Waseem, A. (2021). Vimentin Is at the Heart of Epithelial Mesenchymal Transition (EMT) Mediated Metastasis. *Cancers*, *13*(19), 4985. https://doi.org/10.3390/cancers13194985

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & STROBE Initiative. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Lancet (London, England)*, *370*(9596), 1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X

Wang, H., Wang, L., Song, Y., Wang, S., Huang, X., Xuan, Q., Kang, X., & Zhang, Q. (2017). CD44+/CD24- phenotype predicts a poor prognosis in triple-negative breast cancer. *Oncology Letters*, *14*(5), 5890–5898. https://doi.org/10.3892/ol.2017.6959

Wang, H., Zhang, B., Wang, X., Mao, J., Li, W., Sun, Y., Yuan, Y., Ben, Q., Hua, L., & Qian, A. (2020). TRPV4 Overexpression Promotes Metastasis Through Epithelial-Mesenchymal Transition in Gastric Cancer and Correlates with Poor Prognosis. *OncoTargets and Therapy*, *13*, 8383–8394. https://doi.org/10.2147/OTT.S256918

Wang, J.-Y., Wu, T., Ma, W., Li, S., Jing, W.-J., Ma, J., Chen, D.-M., Guo, X.-J., & Nan, K.-J. (2018). Expression and clinical significance of autophagic protein LC3B and EMT markers in gastric cancer. *Cancer Management and Research*, *10*, 1479–1486. https://doi.org/10.2147/CMAR.S164842

Wang, M., Estrella, J. S., Katz, M. H., Kim, M., Rashid, A., Lee, J. E., Maitra, A., Wistuba, I. I., Wolff, R. A., Varadhachary, G. R., & Wang, H. (2019). Expression of Epithelial-Mesenchymal Transition Markers in Treated Pancreatic Ductal Adenocarcinoma. *Pancreas*, *48*(10), 1367–1372. https://doi.org/10.1097/MPA.0000000000001432

Wang, W., Yi, M., Zhang, R., Li, J., Chen, S., Cai, J., Zeng, Z., Li, X., Xiong, W., Wang, L., Li, G., & Xiang, B. (2018). Vimentin is a crucial target for anti-metastasis therapy of nasopharyngeal carcinoma. *Molecular and Cellular Biochemistry*, *438*(1–2), 47–57. https://doi.org/10.1007/s11010-017-3112-z

Wang, X., Xie, L., & Zhu, L. (2021). Clinicopathological significance of HSP70 expression in gastric cancer: A systematic review and meta-analysis. *BMC Gastroenterology*, *21*(1), 437. https://doi.org/10.1186/s12876-021-01990-4

Wangmo, C., Charoen, N., Jantharapattana, K., Dechaphunkul, A., & Thongsuksai, P. (2020). Epithelial-Mesenchymal Transition Predicts Survival in Oral Squamous Cell Carcinoma. *Pathology Oncology Research: POR*, *26*(3), 1511–1518. https://doi.org/10.1007/s12253-019-00731-z

Whiting, P. F., Rutjes, A. W. S., Westwood, M. E., Mallett, S., Deeks, J. J., Reitsma, J. B., Leeflang, M. M. G., Sterne, J. A. C., Bossuyt, P. M. M., & QUADAS-2 Group. (2011). QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine*, *155*(8), 529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

Wieczorek, E., Lin, Z., Perkins, E. B., Law, D. J., Merchant, J. L., & Zehner, Z. E. (2000). The zinc finger repressor, ZBP-89, binds to the silencer element of the human vimentin gene and complexes with the transcriptional activator, Sp1. *The Journal of Biological Chemistry*, *275*(17), 12879–12888. https://doi.org/10.1074/jbc.275.17.12879

Xia, Y.-Y., Yin, L., Tian, H., Guo, W.-J., Jiang, N., Jiang, X.-S., Wu, J., Chen, M., Wu, J.-Z., & He, X. (2015). HMGA2 is associated with epithelial-mesenchymal transition and can predict poor prognosis in nasopharyngeal carcinoma. *OncoTargets and Therapy*, *8*, 169–176. https://doi.org/10.2147/OTT.S74397

Xiao, S., Liu, L., Fang, M., Zhou, X., Peng, X., Long, J., & Lu, X. (2015). BPTF Associated with EMT Indicates Negative Prognosis in Patients with Hepatocellular Carcinoma. *Digestive Diseases and Sciences*, *60*(4), 910–918. https://doi.org/10.1007/s10620-014-3411-0

Xiao, S., Liu, L., Lu, X., Long, J., Zhou, X., & Fang, M. (2015). The prognostic significance of bromodomain PHD-finger transcription factor in colorectal carcinoma and association with vimentin and E-cadherin. *Journal of Cancer Research and Clinical Oncology*, *141*(8), 1465–1474. https://doi.org/10.1007/s00432-015-1937-y

Xu, B., Jin, D.-Y., Lou, W.-H., & Wang, D.-S. (2013). Lipocalin-2 is associated with a good prognosis and reversing epithelial-to-mesenchymal transition in pancreatic cancer. *World Journal of Surgery*, *37*(8), 1892–1900. https://doi.org/10.1007/s00268-013-2009-6

Yamanaka, C., Wada, H., Eguchi, H., Hatano, H., Gotoh, K., Noda, T., Yamada, D., Asaoka, T., Kawamoto, K., Nagano, H., Doki, Y., & Mori, M. (2018). Clinical significance of CD13 and epithelial mesenchymal transition (EMT) markers in hepatocellular carcinoma. *Japanese Journal of Clinical Oncology*, *48*(1), 52–60. https://doi.org/10.1093/jjco/hyx157

Yamashita, N., Tokunaga, E., Kitao, H., Hisamatsu, Y., Taketani, K., Akiyoshi, S., Okada, S., Aishima, S., Morita, M., & Maehara, Y. (2013). Vimentin as a poor prognostic factor for triple-negative breast cancer. *Journal of Cancer Research and Clinical Oncology*, *139*(5), 739–746. https://doi.org/10.1007/s00432-013-1376-6

Yamazaki, K., Masugi, Y., Effendi, K., Tsujikawa, H., Hiraoka, N., Kitago, M., Shinoda, M., Itano, O., Tanabe, M., Kitagawa, Y., & Sakamoto, M. (2014). Upregulated SMAD3 promotes epithelial-mesenchymal transition and predicts poor prognosis in pancreatic ductal adenocarcinoma. *Laboratory Investigation; a Journal of Technical Methods and Pathology*, *94*(6), 683–691. https://doi.org/10.1038/labinvest.2014.53

Yang, Z., Wang, H., Xia, L., Oyang, L., Zhou, Y., Zhang, B., Chen, X., Luo, X., Liao, Q., & Liang, J. (2017). Overexpression of PAK1 Correlates with Aberrant Expression of EMT Markers and Poor Prognosis in Non-Small Cell Lung Cancer. *Journal of Cancer*, *8*(8), 1484–1491. https://doi.org/10.7150/jca.18553

Yao, J. X., Chen, X., Zhu, Y. J., Wang, H., Hu, X. Y., & Guo, J. M. (2020). Prognostic Value of Vimentin Is Associated With Immunosuppression in Metastatic Renal Cell Carcinoma. *Frontiers in Oncology*, *10*, 1181. https://doi.org/10.3389/fonc.2020.01181

Yeo, C. D., Kang, N., Choi, S. Y., Kim, B. N., Park, C. K., Kim, J. W., Kim, Y. K., & Kim, S. J. (2017). The role of hypoxia on the acquisition of epithelial-mesenchymal transition and cancer stemness: A possible link to epigenetic regulation. *The Korean Journal of Internal Medicine*, *32*(4), 589–599. https://doi.org/10.3904/kjim.2016.302

Yin, S., Chen, F., Ye, P., & Yang, G. (2018). Overexpression of FAM3C protein as a novel biomarker for epithelial-mesenchymal transition and poor outcome in gastric cancer. *International Journal of Clinical and Experimental Pathology*, *11*(8), 4247–4256.

Yin, S., Chen, F.-F., & Yang, G.-F. (2018). Vimentin immunohistochemical expression as a prognostic factor in gastric cancer: A meta-analysis. *Pathology, Research and Practice*, *214*(9), 1376–1380. https://doi.org/10.1016/j.prp.2018.07.014

Yu, Y. T.-C., Chien, S.-C., Chen, I.-Y., Lai, C.-T., Tsay, Y.-G., Chang, S. C., & Chang, M.-F. (2016). Surface vimentin is critical for the cell entry of SARS-CoV. *Journal of Biomedical Science*, *23*(1), 14. https://doi.org/10.1186/s12929-016-0234-7

Yu, Y., Zeng, D., Ou, Q., Liu, S., Li, A., Chen, Y., Lin, D., Gao, Q., Zhou, H., Liao, W., & Yao, H. (2019). Association of Survival and Immune-Related Biomarkers With Immunotherapy in Patients With Non-Small Cell Lung Cancer: A Meta-analysis and Individual Patient-Level Analysis. *JAMA Network Open*, *2*(7), e196879. https://doi.org/10.1001/jamanetworkopen.2019.6879

Zhai, X., Zhu, H., Wang, W., Zhang, S., Zhang, Y., & Mao, G. (2014). Abnormal expression of EMT-related proteins, S100A4, vimentin and E-cadherin, is correlated with clinicopathological features and prognosis in HCC. *Medical Oncology (Northwood, London, England)*, *31*(6), 970. https://doi.org/10.1007/s12032-014-0970-z

Zhang, H., Wu, X., Xiao, Y., Wu, L., Peng, Y., Tang, W., Liu, G., Sun, Y., Wang, J., Zhu, H., Liu, M., Zhang, W., Dai, W., Jiang, P., Li, A., Li, G., Xiang, L., Liu, S., & Wang, J. (2019). Coexpression of FOXK1 and vimentin promotes EMT, migration, and invasion in gastric cancer cells. *Journal of Molecular Medicine (Berlin, Germany)*, *97*(2), 163–176. https://doi.org/10.1007/s00109-018-1720-z

Zhang, L., Li, L., Liu, J., Wang, J., Fan, Y., Dong, B., Zhu, Z., & Zhang, X. (2020). Meta-analysis of multiple hematological biomarkers as prognostic predictors of survival in bladder cancer. *Medicine*, *99*(30), e20920. https://doi.org/10.1097/MD.0000000000020920

Zhang, X., Cao, G., Diao, X., Bai, W., Zhang, Y., & Wang, S. (2022). Vimentin Protein In Situ Expression Predicts Less Tumor Metastasis and Overall Better Survival of Endometrial Carcinoma. *Disease Markers*, *2022*, 5240046. https://doi.org/10.1155/2022/5240046

Zhang, X., Diab, I. H., & Zehner, Z. E. (2003). ZBP-89 represses vimentin gene transcription by interacting with the transcriptional activator, Sp1. *Nucleic Acids Research*, *31*(11), 2900–2914. https://doi.org/10.1093/nar/gkg380

Zhang, X., Wang, Z., Kang, Y., Li, X., Ma, X., & Ma, L. (2014). MCAM expression is associated with poor prognosis in non-small cell lung cancer. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*, *16*(2), 178–183. https://doi.org/10.1007/s12094-013-1057-6

Zhang, Y., Xu, J., Xu, Z., Wang, Y., Wu, S., Wu, L., Song, H., & Zhou, L. (2018). Expression of vimentin and Oct-4 in gallbladder adenocarcinoma and their relationship with vasculogenic mimicry and their clinical significance. *International Journal of Clinical and Experimental Pathology*, *11*(7), 3618–3627.

Zhao, J., Dong, D., Sun, L., Zhang, G., & Sun, L. (2014). Prognostic significance of the epithelial-to-mesenchymal transition markers e-cadherin, vimentin and twist in bladder cancer. *International Braz J Urol: Official Journal of the Brazilian Society of Urology*, *40*(2), 179–189. https://doi.org/10.1590/S1677-5538.IBJU.2014.02.07

Zhao, J., Zhang, L., Dong, X., Liu, L., Huo, L., & Chen, H. (2018). High Expression of Vimentin is Associated With Progression and a Poor Outcome in Glioblastoma. *Applied Immunohistochemistry & Molecular Morphology: AIMM*, *26*(5), 337–344. https://doi.org/10.1097/PAI.0000000000000420

Zhao, W., Jia, L., Kuai, X., Tang, Q., Huang, X., Yang, T., Qiu, Z., Zhu, J., Huang, J., Huang, W., & Feng, Z. (2019). The role and molecular mechanism of Trop2 induced epithelial-mesenchymal transition through mediated β-catenin in gastric cancer. *Cancer Medicine*, *8*(3), 1135–1147. https://doi.org/10.1002/cam4.1934

Zhao, W., Wang, H., Han, X., Ma, J., Zhou, Y., Chen, Z., Zhou, H., Xu, H., Sun, Z., Kong, B., & Fang, H. (2016). ΔNp63α attenuates tumor aggressiveness by suppressing miR-205/ZEB1-mediated epithelial-mesenchymal transition in cervical squamous cell carcinoma. *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine*, *37*(8), 10621–10632. https://doi.org/10.1007/s13277-016-4921-5

Zhao, W., Yue, L., Zhou, F., Xu, C., Liang, W., Sui, A., Ding, A., & Qiu, W. (2013). Clinical significance of vimentin expression and Her-2 status in patients with gastric carcinoma. *Clinical and Translational Science*, *6*(3), 184–190. https://doi.org/10.1111/cts.12043

Zhou, D., Zhang, M., Xu, P., Yu, Y., Ye, G., Zhang, L., & Wu, A. (2016). Expression of pigment epithelium-derived factor is associated with a good prognosis and is correlated with epithelial-mesenchymal transition-related genes in infiltrating ductal breast carcinoma. *Oncology Letters*, *11*(1), 116–124. https://doi.org/10.3892/ol.2015.3880

Zhou, Y., Liao, Q., Han, Y., Chen, J., Liu, Z., Ling, H., Zhang, J., Yang, W., Oyang, L., Xia, L., Wang, L., Wang, H., Xue, L., Wang, H., & Hu, B. (2016). Rac1 overexpression is correlated with epithelial mesenchymal transition and predicts poor prognosis in non-small cell lung cancer. *Journal of Cancer*, *7*(14), 2100–2109. https://doi.org/10.7150/jca.16198

Zhu, Q.-S., Rosenblatt, K., Huang, K.-L., Lahat, G., Brobey, R., Bolshakov, S., Nguyen, T., Ding, Z., Belousov, R., Bill, K., Luo, X., Lazar, A., Dicker, A., Mills, G. B., Hung, M.-C., & Lev, D. (2011). Vimentin is a novel AKT1 target mediating motility and invasion. *Oncogene*, *30*(4), 457–470. https://doi.org/10.1038/onc.2010.421

Zhu, S., Shuai, P., Yang, C., Zhang, Y., Zhong, S., Liu, X., Chen, K., Ran, Q., Yang, H., & Zhou, Y. (2017). Prognostic value of long non-coding RNA PVT1 as a novel biomarker in various cancers: A meta-analysis. *Oncotarget*, *8*(68), 113174–113184. https://doi.org/10.18632/oncotarget.22830

Zuo, J., Wen, J., Lei, M., Wen, M., Li, S., Lv, X., Luo, Z., & Wen, G. (2016). Hypoxia promotes the invasion and metastasis of laryngeal cancer cells via EMT. *Medical Oncology (Northwood, London, England)*, *33*(2), 15. https://doi.org/10.1007/s12032-015-0716-6

8. APPENDIX

8.1. Curriculum Vitae

ÖZGEÇMİŞ

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EDUCATIONAL BACKGROUND

Country	University	Faculty/Institute	Department	Degree	Graduation Year
TC	Mustafa Kemal University	Faculty of Science	Biology	Bachelor's	2011
TC	Cukurova University	Institute of Science	Biotechnology	Masters with thesis	2016

RESEARCH FIELDS

Research Fields
Bioinformatics, Molecular Biology, Data Analysis, Cancer Biology

PUBLICATIONS

Pazarbaşi Hİ, Yılmaz B, Ürünsak İF, Keser N, Korkmaz Güvenmez H (2023) "Association of Infertility and Methylenetetrahydrofolate Reductase Genotypes in Turkish Couples". *Cukurova Medical Journal*, 48(1), pp. 117-26, doi:10.17826/cumj.1193382.
Pazarbaşi Hİ, Pavlopoulou A (2024) "Application of meta-analysis for determining cancer biomarkers" *Archives Medical Review Journal*, 33(3), pp. 165-171, doi:10.17827/aktd.1508230

POSTER PRESENTATIONS

Pazarbaşi Hİ, Ökmen D, Pavlopoulou A (July, 2024) "Vimentin as a prognostic predictor for diverse human cancers: A systematic review and meta-analysis" *17th International Medicine and Health Sciences Researches Congress (UTSAK)*, Ankara, Turkey

8.2. Ethics Committee Report

Institutional review board (or ethics committee) of İzmir Biomedicine and Genome Center (İBG-GOEK)

İZMİR BİYOTIP VE GENOM MERKEZİ
GİRİŞİMSEL OLMAYAN ARAŞTIRMALAR ETİK KURULU (İBG-GOEK)
KARARI

Toplantı Tarihi	: 26/03/2021	**Toplantı Günü**	: Cuma
Toplantı Sayısı	: 4	**Toplantı Saati**	: 10:30

Sayın Doçent Doktor Duygu SAĞ WINGENDER,

2021-010 Protokol No'lu; sorumlusu olduğunuz "Vimentinin kanser prognozu ve teşhisinde rolünü araştırmak için hesaplamalı yöntemlerin uygulanması" başlıklı araştırmanın uygulanmasında etik açıdan sakınca olmadığına oy birliği ile karar verilmiştir.

Bilgilerinizi ve gereğini rica ederiz.

Prof. Dr. H. Alper BAĞRIYANIK
Başkan

Pandemi süresince online ortamda gerçekleştirilen toplantımızda alınan kararlar tek imzalı olarak düzenlenmektedir. Pandemi sona erdikten sonra ıslak imzalı karar belgesi teslim edilecektir.

8.3. Publications from the Thesis

Pazarbaşi Hİ, Pavlopoulou A (2024) “Application of meta-analysis for determining cancer biomarkers” *Archives Medical Review Journal*, 33(3), pp. 165-171, doi:10.17827/aktd.1508230

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Application of meta-analysis for determining cancer biomarkers

Kanser biyobelirteçlerinin belirlenmesi için meta-analizin uygulanması

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ABSTRACT
The health care professionals are facing the challenge to combine and translate the findings from a plethora of, often conflicting, clinical trials or clinical studies in order to reach an evidence-based decision. The application of a meta-analytical approach in the medical field allows the systematic synthesis and assessment of the results across studies to draw conclusions about the main body of the research, such as a more accurate estimate of treatment effect or determining disease risk factors. Herein, we review the advantages and the basic steps of meta-analysis towards the identification of powerful cancer biomarkers.
Keywords: Meta-analysis; cancer; biomarkers

ÖZET
Sağlık uzmanları, kanıta dayalı bir karara varmak için çok sayıda, çoğu zaman birbiriyle çelişen klinik araştırmalardan elde edilen bulguları birleştirme ve tercüme etme zorluğuyla karşı karşıyadır. Meta-analitik yaklaşımların tıp alanında uygulanması, tedavi etkisinin daha doğru tahmin edilmesi veya hastalık risk faktörlerinin belirlenmesi gibi araştırmanın ana kısmı hakkında sonuçlar çıkarmak için çalışmalardaki sonuçların sistematik sentezine ve değerlendirilmesine olanak tanır. Bu çalışmada, güçlü kanser biyobelirteçlerinin tanımlanmasına yönelik meta-analizin avantajlarını ve temel adımlarını derleyeceğiz.
Anahtar kelimeler: Meta-analiz, kanser, biyobelirteçler

Introduction

The need for identifying powerful biomarkers for the accurate and timely diagnosis, prognosis and evidence-based decision making for diverse types of cancers poses a major challenge in clinical and medical research[1-5]. Given the continuous accumulation of quantitative and qualitative data from clinical trials and studies, meta-analysis has emerged as a fundamental tool in clinical practice and public health for data collection, evaluation, and interpretation, in order to obtain statistically significant and relevant information at low cost. Meta-analysis is the application of statistical methods to combine the quantitative findings from multiple scientific studies, addressing the same question, so as to increase statistical power over individual studies, and to deal with any conflict among the individual studies[6-8].

In this minireview, we provide a methodological guide for conducting meta-analyses by using transparent and reproducible ways to draw valid conclusions from the body of the research.

Defining the research question

The first step in carrying out a meta-analysis is the formulation of a clear and well-articulated research question[9]. For example, is *HOTAIR* expression associated with survival in human cancers? The researchers should provide a background of the topic, referring to the current state of knowledge, and state precisely the main goals of the meta-analysis. In the meta-analysis conducted by Toy and colleagues (2019), the authors discuss the gaps in the scientific literature and specify specify the research objectives, i.e. to perform a comprehensive and updated meta-analysis in order to investigate the prognostic value of *HOTAIR* expression in cancer [10]. In this way, a significant positive correlation between *HOTAIR* overexpression and

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poor overall survival, as well as progression/metastasis-free and recurrence/disease-free survival, was found in multiple and diverse types and subtypes of human cancers[10].

Systematic Literature Review

The systematic review of relevant studies for collecting published and unpublished information is a difficult task of meta-analysis. To maximize the number of the retrieved pertinent studies, it is recommended to search more than one of the bibliographic databases such as MEDLINE/PubMed, Scopus, Embase, The Cochrane Central Register of Controlled Trial, Web of Science, Google Scholar[11].

An extensive, usually manual, search of the scientific databases is performed by using a combination of relevant search terms. Initially, the title and abstract of the articles are scanned and the irrelevant studies are excluded from the subsequent steps of the analysis. The reference list of the review articles can be also examined to identify other articles that were omitted in the initial search. The included articles are then subjected to a selection filter based on established inclusion (English language of publication, minimal sample size etc.) and exclusion (not original research, inadequate sample size, etc.) criteria. The key variables to be extracted from the eligible studies should be defined. Broad inclusion criteria would increase heterogeneity among studies, whereas narrow inclusion criteria would limit the number of pertinent studies[8,12].

Furthermore, assessment of the quality of the included studies, could assist reviewers in determining the inclusion/exclusion criteria or the representativeness of the study sample. For example, the Jadad scale[13] is often used for assessing the quality of randomized clinical trials, Newcastle-Ottawa scale[14,15] for non-randomized studies, AXIS for cross-sectional studies[16], and QUADAS-2 for the quality assessment of diagnostic accuracy studies[17].

The key data are extracted from the primary articles and recorded in a structured form, usually in an ad hoc Excel spreadsheet. In the case key data are not available in the main text or the supplementary material of the primary research article, it is advised to contact the corresponding authors to ask for any missing data. In addition, it is recommended that the above mentioned tasks are carried out by two investigators independently and potential dispute is resolved by consensus[8,12,18].

The process of ensuring the transparency, reliability, comprehensiveness, and replicability of a systematic review is facilitated by updated reporting guidelines, established by international consortia. Examples of these guidelines for systematic reviews include QUORUM (Quality of Reporting of Meta-analyses)[19], MOOSE (Meta-analysis Of Observational Studies in Epidemiology)[20], and the most widely used PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist[21]. Moreover, guidelines have been developed for reporting certain sorts of evidence and information, such as CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized clinical trials[22], STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for various types of observational clinical studies (usually in the surgical discipline)[23], meta-analysis methods for genetic association studies[24] as well as genome-wide association studies[25].

Statistical analyses

Statistical analyses are performed on the collected data. There are several state-of-the-art, freely accessible statistical analysis software such as Stata (https://www.stata.com/) or R (https://www.r-project.org/) or standalone applications.

Effect Estimation

Selecting the appropriate effect measure depends on the types of data, i.e. dichotomous (or binary) data, continuous data, time-to-event data etc. Many epidemiological studies measure binary outcomes using defined endpoints. In this case, the overall effect can be measured by odds ratio (OR), relative risk (RR) and risk difference (RD).

The odds ratio (OR)[26,27] measures the association between two events, i.e., exposure and outcome, in case-control studies. OR is defined as the ratio of the odds of an outcome in the presence of a particular exposure

and the odds of the outcome in the absence of this exposure; OR higher that 1 indicates that the outcome (e.g. survival) is more likely to occur in the presence of a given exposure (e.g. treatment). For example, Zhu and coworkers (2017) used OR to show that PVT1 expression is significantly correlated with lymph node metastasis (OR=2.67, 95% CI: 1.66–4.29), distant metastases (OR=4.00, 95% CI: 1.39–11.50), advanced tumor-node-metastasis (TNM) stage (OR=3.28, 95%CI: 2.46–4.38), and tumor size (OR=1.47, 95% CI: 1.02–2.11)[28]. Moreover, Wang et al. (2021) found that heat shock protein 70 (HSP70) expression is robustly associated with higher tumor differentiation, (OR = 0.49, 95%CI: 0.37–0.65), intestinal gastric cancer (OR = 2.19, 95%CI : 1.59–3.01) and lymphovascular invasion (OR = 1.54, 95%CI: 1.19–2.00; invasion[29].

RR or risk ratio[27,30] is the ratio of the risk probability of an event in the presence of exposure to the risk probability of this event in the absence of the same exposure. Nassour et al. (2023) found that there is a higher RR of bladder and kidney cancer in Lynch syndrome patients[31].

Another metric, RD[32], is the difference between the risk of an event in the presence and the absence of a specific exposure. For example, in a recent study, Nakamura et al. (2024) demonstrated that the heat-shock protein HSP40 is associated with a lower probability (RD = 0.18, 95%CI: 0.03-0.33) and HSF1 (RD = -0.16, 95%CI: -0.29 to -0.04) with a higher probability of lymph node dissemination[33].

Hazard ratio (HR)[34] metric is usually applied for time-to-event data. HR measures the hazard rate of an event (e.g. survival rate) in an exposed group (e.g. treated) compared to the hazard rate of the same event in an unexposed group (e.g. untreated). HR is most often used in survival studies since it represents the instantaneous risk at different time points of the entire study period, unlike OD, RR and RD, which are cumulative over the length of the study. In case the HR is not reported in the article, it can be estimated from the survival curves (i.e. Kaplan-Meier curves) with the Cox proportional hazards model[35]. For example, in a comprehensive meta-analysis by Toy and colleagues (2019), the HR in cancer patients with high *HOTAIR* expression was estimated to be greater than 1, indicating that the overall survival rate of the patients over-expressing *HOTAIR* is lower compared to those with low *HOTAIR* expression[10]. Fang et al. (2020) found a significant positive correlation between elevated *lncSNHG15* expression and poor overall (HR = 2.07, 95%CI, 1.48-2.88) and disease-free (HR = 2.32, 95%CI: 1.53-3.53;) survival[36]. In a recent study, de Moraes and collaborators (2024) showed that the progression-free survival rate is higher in the breast cancer patients treated only with CDK inhibitors (CDKi) compared to those treated with CDKi and PPI (HR = 2.0901, 95%CI: 1.410-2.9498)[37].

Forest Plot

The results of the meta-analyses are typically presented using forest plots[38] (Figure 1), a graphical display of the estimated effect sizes for each study with the corresponding 95% confidence interval (95%CI), as well as the pooled or overall effect, which is the weighted average of the individual estimates.

Selection of the best fit statistical model

Most meta-analyses are based on two statistical models, fixed- or random-effect model[39], to calculate the overall effect. The fixed-effects model assumes that studies share a single common true effect size, and the overall effect is an estimate of the common effect size. The random-effects model assumes that true effects vary among studies and the overall effect is the weighted average of the effects reported in the individual studies.

Heterogeneity

The studies included in a meta-analysis have inherent considerable differences due to the overall design, methodology, data processing and analysis etc. Heterogeneity represents the degree of disagreement among studies in a meta-analysis, which is essential to be detected and measured in order to determine whether the heterogeneity is acceptable and, hence, appropriate to combine these studies in the meta-analysis or not. Several heterogeneity metrics are applied to assess heterogeneity[40,41].

Cochran's Q test[42] is a non-parametric (chi-square) statistical test used to examine whether all studies have the same effect. The Q test calculates the sum of the weighted squared differences between the effects of

the individual studies and the overall effect. The null hypothesis is rejected if the Q test p-value is less than 0.05, indicating the presence of heterogeneity. Another robust metric, the Higgins I^2 statistic[43] estimates the percentage of observed total variation across studies that is attributed to real heterogeneity rather than random chance. I^2 is calculated with the formula $(Q-df)/Q\times100\%$, where 'Q' is the Cochran test and 'df' is the degrees of freedom. I^2 values range between 0% (indicating lack of heterogeneity) and 100% (indicating high level of heterogeneity). Generally, if there is high heterogeneity ($I^2 \geq 50\%$), the random-effects model is applied; alternatively, if the heterogeneity is low ($I^2 < 50\%$), the fixed-effects model is used[10].

Subgroup analysis[44] is a method often used to assess heterogeneity. The studies are divided into groups based on certain features and characteristics (e.g. data extraction method, ethnicity, income). Separate meta-analyses are conducted for each subgroup in order to detect any statistically significant differences among the subgroups.

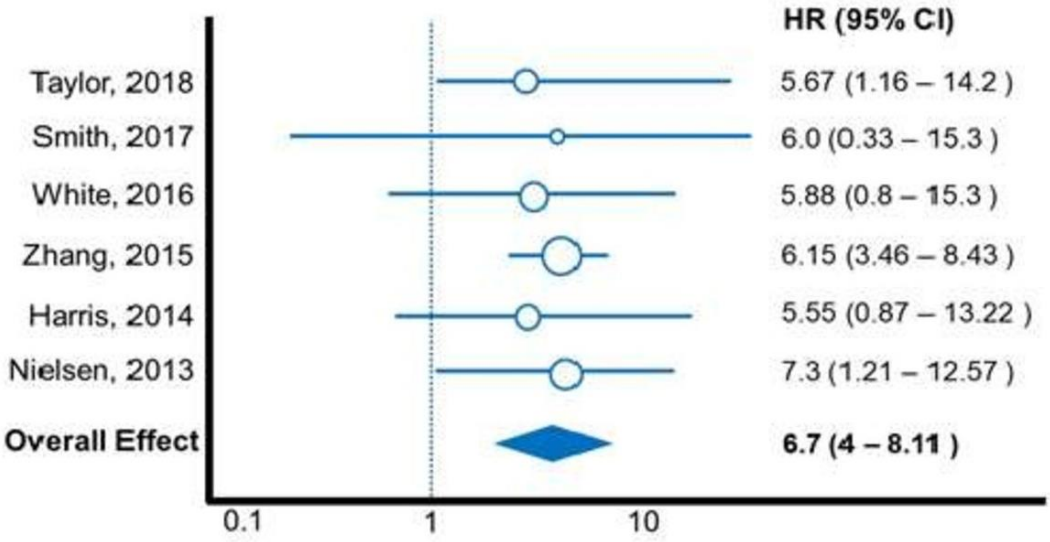

Figure 1. Example forest plot of hazard ratios. On the left column, the individual studies (indicated by the first author's name and the date) are shown in chronological order. The measure of the effect for each of these studies is indicated by circles, incorporating 95%CI (represented by whiskers). The marker's size is proportional to the study's weight in the meta-analysis; larger sample sizes are given more weight. The overall effect is represented by a diamond and the width of the diamond reflects the 95%CI of the estimate.

Sensitivity analysis

Sensitivity analysis is performed to verify the consistency of outcomes (Figure 2), and it is conducted by consecutively omitting one study, repeating the meta-analysis, and examining the effect of the excluded study on the overall effect. In case an individual study has an impact on the overall effect size this study most likely accounts for the between-study variability. For instance, in a meta-analytical study by Bonovas and colleagues (2008), where the association of statins with the risk for pancreatic cancer was investigated, a particular study was found to contribute mostly to the between study variation; when this study was excluded from the subsequent analysis, the heterogeneity was markedly reduced[45].

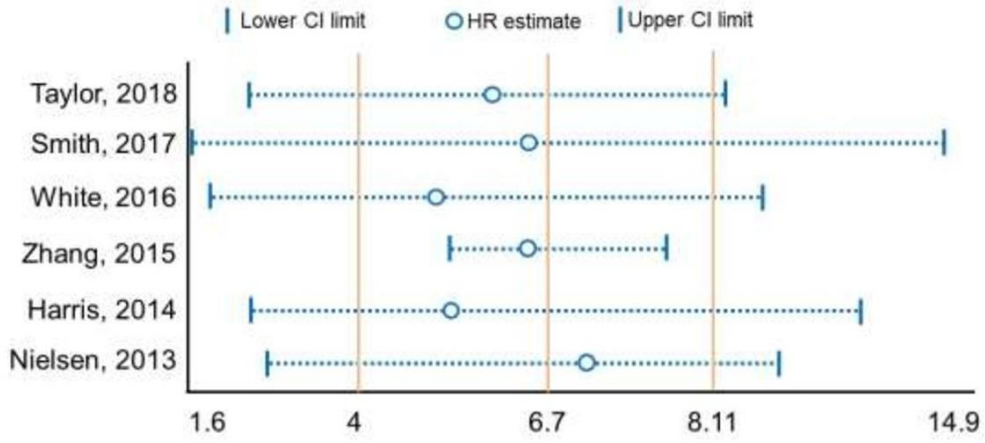

Figure 2. Example sensitivity analysis. There is no alteration in the results due to the inclusion of any individual study; the pooled HR and 95%CI remain the same.

Publication bias

Publication bias[46] is a major aspect of concern in meta-analyses, since there is less probability of studies with non statistically significant results being published than significant findings. Thus, assessing the presence and potential effects of publication bias is critical for ensuring validity and reliability of the outcome[9,47]. There are several methods to deal with publication bias in meta-analyses[48].

A quasi-statistical approach, the funnel plot [49], is a scatterplot which allows the visual inspection of the presence of publication bias. In the funnel plot, the standard errors of the effect estimates of the individual studies are plotted on the horizontal axis versus the standard error of the estimated effect on the vertical axis. A symmetrical or asymmetrical inverted funnel plot indicates the absence or presence of publication bias, respectively (Figure 3). In a funnel plot, small studies have a tendency to be more widely scattered at the bottom of the funnel plot, whilst larger studies typically have narrower spread, since they are more precise and are closer to the true effect size.

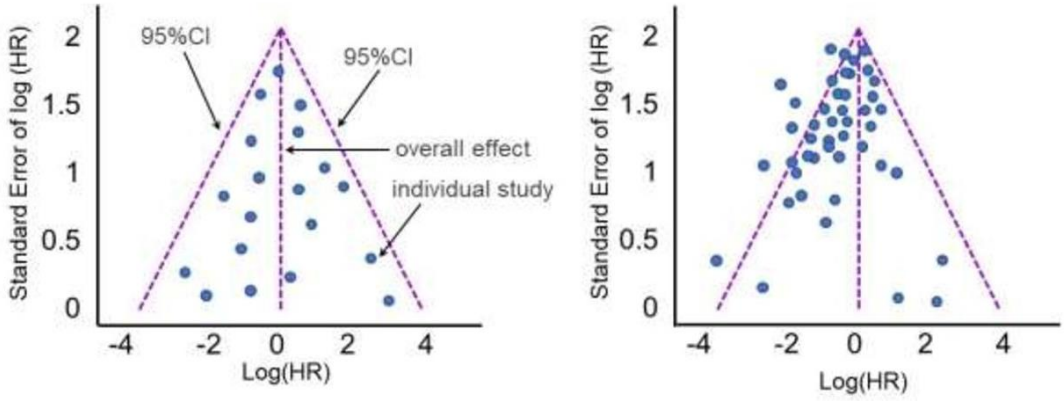

Figure 3. Example funnel plots. Left: symmetrical funnel plot. Right: asymmetrical funnel plot.

The Begg-Mazumdar adjusted rank correlation test can be also employed to identify any significant correlation between the effect estimates and their variances; this test is a statistical analogue of the funnel plot[50]

Egger's test[49] is also used to perform a linear regression of the standardized effect estimates on their standard errors; a p-value less than 0.05 indicates statistically significant publication bias.

Conclusion

Herein, we describe the core methodology and statistical techniques most commonly used to conduct meta-analyses for the discovery of potential cancer biomarkers. These biomarkers can be diagnostic molecular markers, prognostic predictors, disease monitoring biomarkers or predictors of response to therapy. Meta-analysis enables the investigators to synthesize the outcomes of diverse studies accurately and systematically, deal with controversies arising from conflict among studies and meaningfully interpret the available biological or epidemiological data, towards addressing the needs of the patients and the oncology healthcare systems.

References

1. Das S, Dey MK, Devireddy R, Gartia MR. Biomarkers in Cancer Detection, Diagnosis, and Prognosis. Sensors (Basel). 2023;24.
2. Liu Z, Zhang Y, Niu Y, Li K, Liu X, Chen H et al. A systematic review and meta-analysis of diagnostic and prognostic serum biomarkers of colorectal cancer. PLoS One. 2014;9:e103910.
3. Yu Y, Zeng D, Ou Q, Liu S, Li A, Chen Y et al. Association of Survival and Immune-Related Biomarkers With Immunotherapy in Patients With Non-Small Cell Lung Cancer: A Meta-analysis and Individual Patient-Level Analysis. JAMA Netw Open. 2019;2:e196879.
4. Zhang L, Li L, Liu J, Wang J, Fan Y, Dong B et al. Meta-analysis of multiple hematological biomarkers as prognostic predictors of survival in bladder cancer. Medicine (Baltimore). 2020;99:e20920.
5. Fountzilas E, Vo HH, Mueller P, Kurzrock R, Tsimberidou AM. Correlation between biomarkers and treatment outcomes in diverse cancers: a systematic review and meta-analysis of phase I and II immunotherapy clinical trials. Eur J Cancer. 2023;189:112927.
6. Shadish WR, Lecy JD. The meta-analytic big bang. Res Synth Methods. 2015;6:246-64.
7. Papakostidis C, Giannoudis PV. Meta-analysis. What have we learned? Injury. 2023;54:30-34.
8. Forero DA, Lopez-Leon S, Gonzalez-Giraldo Y, Bagos PG. Ten simple rules for carrying out and writing meta-analyses. PLoS Comput Biol. 2019;15:e1006922.
9. Shaheen N, Shaheen A, Ramadan A, Hefnawy MT, Ramadan A, Ibrahim IA et al. Appraising systematic reviews: a comprehensive guide to ensuring validity and reliability. Front Res Metr Anal. 2023;8:1268045.
10. Toy HI, Okmen D, Kontou PI, Georgakilas AG, Pavlopoulou A. HOTAIR as a Prognostic Predictor for Diverse Human Cancers: A Meta- and Bioinformatics Analysis. Cancers (Basel). 2019;11.
11. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. FASEB J. 2008;22:338-42.
12. Nikolopoulos GK, Bagos PG, Bonovas S. Developing the evidence base for cancer chemoprevention: use of meta-analysis. Curr Drug Targets. 2011;12:1989-97.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12.
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-5.
15. Moskalewicz A, Oremus M. No clear choice between Newcastle-Ottawa Scale and Appraisal Tool for Cross-Sectional Studies to assess methodological quality in cross-sectional studies of health-related quality of life and breast cancer. J Clin Epidemiol. 2020;120:94-103.
16. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open. 2016;6:e011458.
17. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529-36.
18. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: pitfalls and hints. Heart Lung Vessel. 2013;5:219-25.
19. Clarke M. The QUORUM statement. Lancet. 2000;355:756-7.
20. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surg. 2021;156:787-88.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
22. Cuschieri S. The CONSORT statement. Saudi J Anaesth. 2019;13:27-30.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-9.
24. Sagoo GS, Little J, Higgins JP. Systematic reviews of genetic association studies. Human Genome Epidemiology Network. PLoS Med. 2009;6:e28.
25. Evangelou E, Ioannidis JP. Meta-analysis methods for genome-wide association studies and beyond. Nat Rev Genet. 2013;14:379-89.
26. Szumilas M. Explaining odds ratios. J Can Acad Child Adolesc Psychiatry. 2010;19:227-9.

27. Ranganathan P, Aggarwal R, Pramesh CS. Common pitfalls in statistical analysis: Odds versus risk. Perspect Clin Res. 2015;6:222-4.
28. Zhu S, Shuai P, Yang C, Zhang Y, Zhong S, Liu X et al. Prognostic value of long non-coding RNA PVT1 as a novel biomarker in various cancers: a meta-analysis. Oncotarget. 2017;8:113174-84.
29. Wang X, Xie L, Zhu L. Clinicopathological significance of HSP70 expression in gastric cancer: a systematic review and meta-analysis. BMC Gastroenterol. 2021;21:437.
30. Sistrom CL, Garvan CW. Proportions, odds, and risk. Radiology. 2004;230:12-9.
31. Nassour AJ, Jain A, Hui N, Siopis G, Symons J, Woo H. Relative Risk of Bladder and Kidney Cancer in Lynch Syndrome: Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15.
32. Kim HY. Statistical notes for clinical researchers: Risk difference, risk ratio, and odds ratio. Restor Dent Endod. 2017;42:72-76.
33. Nakamura ET, Park A, Pereira MA, Kikawa D, Tustumi F. Prognosis value of heat-shock proteins in esophageal and esophagogastric cancer: A systematic review and meta-analysis. World J Gastrointest Oncol. 2024;16:1578-95.
34. Roberts MR, Ashrafzadeh S, Asgari MM. Research Techniques Made Simple: Interpreting Measures of Association in Clinical Research. J Invest Dermatol. 2019;139:502-11 e1.
35. Tibshirani R. A plain man's guide to the proportional hazards model. Clin Invest Med. 1982;5:63-8.
36. Fang SX, Chen C, Guo Q, Ke XX, Lu HL, Xu G. High lncSNHG15 expression may predict poor cancer prognosis: a meta-analysis based on the PRISMA and the bio-informatics analysis. Biosci Rep. 2020;40.
37. de Moraes FCA, Pereira CRM, Sano VKT, Laia EA, Stecca C, Burbano RMR. Do proton pump inhibitors affect the effectiveness of cyclin-dependent kinase 4/6 inhibitors in advanced HR positive, HER2 negative breast cancer? A meta-analysis. Front Pharmacol. 2024;15:1352224.
38. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. BMJ. 2001;322:1479-80.
39. Dettori JR, Norvell DC, Chapman JR. Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. Global Spine J. 2022;12:1624-26.
40. Sedgwick P. Meta-analyses: what is heterogeneity? BMJ. 2015;350:h1435.
41. Cordero CP, Dans AL. Key concepts in clinical epidemiology: detecting and dealing with heterogeneity in meta-analyses. J Clin Epidemiol. 2021;130:149-51.
42. Cochran WG. The comparison of percentages in matched samples. Biometrika. 1950;37:256-66.
43. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
44. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: A tutorial Clinical Epidemiology and Global Health. 2019;7:192-98.
45. Bonovas S, Filioussi K, Sitaras NM. Statins are not associated with a reduced risk of pancreatic cancer at the population level, when taken at low doses for managing hypercholesterolemia: evidence from a meta-analysis of 12 studies. Am J Gastroenterol. 2008;103:2646-51.
46. Sedgwick P. What is publication bias in a meta-analysis? BMJ. 2015;351:h4419.
47. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74:785-94.
48. Jin ZC, Zhou XH, He J. Statistical methods for dealing with publication bias in meta-analysis. Stat Med. 2015;34:343-60.
49. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.
50. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-101.

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