Prognostic value of high IMP3 expression in solid tumors: a meta-analysis

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Background: Accumulated studies have investigated the prognostic role of insulin-like growth factor II mRNA-binding protein 3 (IMP3) in various cancers, but inconsistent and controversial results were obtained. Therefore, we performed a systematic review and meta-analysis to investigate the potential value of IMP3 in the prognostic prediction of human solid tumors.

Materials and methods: A systematic literature search in the electronic databases PubMed, Embase, Web of Science, and Cochrane library (updated to April 2016) was conducted to identify eligible studies. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) for survival outcomes were calculated and gathered using STATA 12.0 software.

Results: A total of 53 studies containing 8,937 patients with solid tumors were included in this meta-analysis. High IMP3 expression was significantly associated with worse overall survival (OS) of solid tumors (HR = 2.08, 95% CI: 1.80–2.42, P < 0.001). Similar results were observed in cancer-specific survival (CSS), disease-free survival (DFS), recurrence-free survival (RFS), progression-free survival (PFS), and metastasis-free survival (MFS). Further subgroup analysis stratified by tumor type showed that elevated IMP3 expression was associated with poor OS in renal cell carcinoma (RCC), lung cancer, oral cancer, urothelial carcinoma, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer, gastric cancer, and intrahepatic cholangiocarcinoma (ICC).

Conclusion: The current evidence suggests that high IMP3 expression is associated with poor prognosis in most solid tumors. IMP3 is a potential valuable prognostic factor and might serve as a promising biomarker to guide clinical decisions in human solid tumors.

Keywords: IMP3, prognosis, solid tumor, biomarker, meta-analysis

Introduction
Insulin-like growth factor II mRNA-binding protein 3 (IMP3 or IGF2BP3) is a member of the RNA-binding protein family, which plays an important role in RNA trafficking and stabilization, cell growth, and cell migration during the early stages of embryogenesis. IMP3 was proposed to control the translation or turnover of various candidate target genes, including IGF2, CD44, HMGA2, and MMP9. This oncofetal protein has been reported to promote tumor cell survival, proliferation, chemoresistance, and tumor cell invasiveness in vitro. In recent years, accumulating studies have shown that IMP3 is specifically expressed in malignant tumors and acts as an important cancer-specific gene involved in many aggressive and advanced cancers.

Numerous studies have reported that upregulated IMP3 expression in tumor tissues is correlated with poor patient survival and can be used as a prognostic factor to guide clinical decisions and distinguish different prognoses in various solid tumors, such as renal cell carcinoma (RCC), lung cancer, oral cancer, bladder cancer, gastrointestinal tumors, and gynecological tumors. However, some other studies have reported
the absence of association between IMP3 expression and cancer prognosis.\textsuperscript{14,15} Some investigators have also replayed completely opposite results in ovarian cancer. For instance, Kobel et al\textsuperscript{16} proposed that IMP3 expression is a marker of unfavorable prognosis, whereas Noske et al\textsuperscript{17} asserted that IMP3 expression is associated with improved survival. Hence, the prognostic role of IMP3 expression in solid tumors remains unclear and controversial.

Therefore, we conducted a systematic review of published studies, with a standard meta-analysis combining available evidence, to evaluate the prognostic value of IMP3 expression in solid tumors.

Materials and methods
This meta-analysis was conducted according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)\textsuperscript{18} (Table S1). Because the data included in this study were retrieved from published articles, ethical approval from ethics committees was not needed.

Literature search
A comprehensive literature search was performed in PubMed, Embase, Web of Science, and Cochrane Library to identify studies evaluating IMP3 expression and clinical prognosis in solid tumors up to April 2016. The search strategy included the following terms through MeSH headings, keywords, and text words: “IMP3” or “Insulin-like growth factor 2 mRNA binding protein 3” or “IGF2BP3” combined with “cancer” or “carcinoma” or “neoplasm”. The references cited in the identified articles were also screened for possible inclusions. The database search and preliminary evaluation of identified studies were performed independently by two investigators (LC and YX). No language limitation existed in the process.

Study selection
The inclusion criteria for selecting articles in our analysis are listed as follows: 1) studies that reported IMP3 expression in cancer tissues, 2) studies analyzing the relationship between IMP3 expression level and clinical cancer outcomes, 3) studies that directly reported survival outcomes with hazard ratio (HR) and corresponding 95% confidence interval (CI) or studies that provided sufficient data for estimating HR and 95% CI by using the methods described by Tierney et al,\textsuperscript{19} and 4) studies with a median follow-up of at least 6 months. Studies were excluded if they were 1) case reports, letters, conference abstracts, or reviews, 2) non-human research, 3) investigations on the diagnostic role, but not the prognostic role, of IMP3, and 4) studies with insufficient data for calculating the HR and 95% CI. If duplicate publications by the same authors were retrieved, we included only the most informative and recent study. Two independent reviewers (LC and YX) evaluated the full articles for study eligibility, and any disagreement was resolved by consensus.

Data extraction and quality assessment
Two authors (LC and YX) independently extracted data from each eligible study by using predefined item forms. The following information, if available, was recorded: first author’s name, year of publication, study country or region, type of cancer, cancer stage, number of patients, detected method, cutoff definition, percentage of high IMP3 expression, follow-up period, and survival outcomes with their HRs and corresponding 95% CIs. If univariate and multivariate analyses were reported to obtain the HRs, the results of multivariate analysis were preferentially selected. If HRs and 95% CIs were not provided directly, we attempted to estimate these points with Kaplan–Meier curve or other required data in the original study by using Tierney et al’s methods.\textsuperscript{19} Study quality was scored by two investigators (LC and YX) using the Newcastle–Ottawa Scale, which involves three main categories: selection, comparability, and outcome ascertainment. We defined studies with scores no less than 6 as qualified to be included in the meta-analysis. Discrepancies between investigators were resolved through discussion.

Statistical analysis
Pooled HRs and corresponding 95% CIs were calculated to evaluate the prognostic role of high IMP3 expression in the clinical outcomes of solid tumors. An observed HR greater than 1 implied a worse prognosis in patients with high IMP3 expression, and an HR less than 1 indicated a better prognosis. Statistical heterogeneity of combined HR was assessed using Cochrane \( Q \)-test and Higgins \( I^2 \) metrics. \( I^2>50\% \) was considered a measure of obvious heterogeneity.\textsuperscript{20} If no evident heterogeneity existed, the fixed-effect model (Mantel–Haenszel method) was used to pool the results.\textsuperscript{21} Otherwise, the random-effect model (DerSimonian and Laird method) was selected.\textsuperscript{22} The potential sources for heterogeneity, if significant, were further explored using a predefined subgroup analysis and meta-regression analysis (based on cancer type, ethnicity, case number, cutoff, cancer stage, HR obtained method, and analysis method). To assess the stability of the pooled results, sensitivity analysis was performed by sequential omission of each single study. Publication bias was also estimated by
visually assessing the asymmetry of the funnel plot and then quantitatively evaluated by Begg’s and Egger’s tests.\textsuperscript{23,24} All the abovementioned analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA). All statistical tests were two sided, and statistical significance was defined as a P-value less than 0.05.

**Results**

**Search results and study characteristics**

The flowchart of the literature search is shown in Figure 1. A total of 420 potentially relevant studies were retrieved from the initial literature search in the aforementioned electronic databases. A total of 144 duplicated records were excluded by a literature manager software. After carefully screening titles and abstracts of the remaining 120 records, 46 studies were excluded and 74 studies were selected for full-text assessment. Given the inclusion and exclusion criteria, 21 studies that belonged to duplicate publication or failed to offer sufficient prognostic information were excluded. Finally, 53 studies satisfied our eligibility criteria and were included in this meta-analysis.

The characteristics of these enrolled studies are summarized in Table 1. The 53 studies involved 8,937 patients with different cancer types, including 6 studies of RCC,\textsuperscript{8,25–29} 6 lung cancer,\textsuperscript{9,30–34} 4 oral cancer,\textsuperscript{10,35–37} 4 urothelial carcinoma,\textsuperscript{38–41} 4 ovarian cancer,\textsuperscript{16,17,42,43} 3 hepatocellular carcinoma (HCC),\textsuperscript{44–46} 4 colorectal cancer,\textsuperscript{12,47–49} 3 prostate cancer,\textsuperscript{14,15,50} 3 pancreatic cancer,\textsuperscript{51–53} 2 gastric cancer,\textsuperscript{11,54} 2 intrahepatic cholangiocarcinoma (ICC),\textsuperscript{55,56} and one study each of tongue cancer,\textsuperscript{57} thyroid carcinoma,\textsuperscript{58} sacral chordoma,\textsuperscript{59} pilocytic astrocytoma and pilomyxoid astrocytoma (PA/PMA),\textsuperscript{60} neuroblastoma,\textsuperscript{61} meningioma,\textsuperscript{62} melanoma,\textsuperscript{63} breast cancer,\textsuperscript{64} giant cell tumor,\textsuperscript{65} bile duct carcinoma,\textsuperscript{66} esophageal carcinoma,\textsuperscript{67} and cervical cancer.\textsuperscript{13} A total of 25 studies involved Caucasians and 28 involved Asians. The survival outcomes in these studies, including overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), recurrence-free survival (RFS), progression-free survival (PFS), and metastasis-free survival (MFS), were investigated in 40, 10, 8, 7, 4, and 5 studies, respectively. HRs were reported directly in most of these studies (43/53) and were estimated indirectly in the 10 other studies. Multivariate Cox

![Flowchart of the study selection process.](image-url)
| Author                | Year | Country or region | Cancer type | Case number | Method | Cutoff | High expression | Follow-up     | Outcomes | Analysis | HR obtained | NOS score |
|-----------------------|------|-------------------|-------------|-------------|--------|--------|-----------------|---------------|----------|----------|-------------|-----------|
| Jiang et al³⁸         | 2006 | USA               | RCC         | 371         | IHC    | Positive vs negative¹ | 71 (19.1%) | Median 63 months | OS MFS       | Multi    | Report    | 9          |
| Poj et al³⁶           | 2015 | USA               | RCC         | 346         | IHC    | Positive vs negative  | 73 (21.1%) | > 10 years       | OS RFS       | Multi    | Report    | 8          |
| Hoffmann et al²⁵      | 2008 | USA               | RCC         | 716         | IHC    | Positive vs negative  | 213 (29.7%) | 9.5 years       | CSS MFS      | Multi    | Report    | 8          |
| Park et al¹⁴          | 2014 | Korea             | RCC         | 148         | IHC    | > 5% of cells stained | 43 (29.1%) | Median 55.5 months | CSS         | Multi    | Report    | 7          |
| Jiang et al³⁸         | 2008 | USA               | RCC         | 317         | IHC    | Positive vs negative  | 40 (12.6%) | 8.8 years       | OS MFS       | Multi    | Report    | 9          |
| Tantravahi et al²⁷    | 2015 | USA               | RCC         | 27          | IHC    | > 20% of cells stained | 14 (51.9%) | > 2 years       | OS           | Multi    | Report    | 6          |
| Del Gobbo et al³⁴     | 2014 | Italy             | Lung cancer | 74          | IHC    | Positive vs negative  | 24 (32.4%) | Mean 65.6 months | OS DFS       | Uni      | Report    | 7          |
| Sun et al²³           | 2015 | China             | Lung cancer | 196         | IHC    | H-score > 100 (0–300) | 83 (42.3%) | Range (16.5–69.0) months | OS DFS       | Multi    | Report    | 8          |
| Yan et al³⁰           | 2015 | China             | Lung cancer | 95          | IHC    | > 25% of cells stained | 39 (41.1%) | > 5 years       | OS           | Multi    | Report    | 7          |
| Zhang et al³³         | 2015 | China             | Lung cancer | 186         | IHC    | > 5% of cells stained | 139 (74.7%) | > 5 years       | OS           | Multi    | Report    | 8          |
| Lin et al³⁰           | 2015 | China             | Lung cancer | 92          | IHC    | Positive vs negative  | 62 (67.4%) | > 5 years       | OS           | Multi    | Report    | 8          |
| Beljan Perak et al³¹  | 2012 | Croatia           | Lung cancer | 90          | IHC    | > 10% of cells stained | 61 (67.8%) | > 5 years       | OS           | Uni      | SC        | 6          |
| Clauditz et al³³      | 2013 | Germany           | Oral cancer | 145         | IHC    | > 10% of cells stained | 79 (54.5%) | Mean 41.3 months | OS           | Multi    | Report    | 8          |
| Lin et al³⁷           | 2011 | Taiwan            | Oral cancer | 93          | IHC    | > 25% of cells stained | 51 (54.8%) | Mean 44.8 months | OS           | Multi    | Report    | 9          |
| Li et al³⁹            | 2010 | Korea             | Oral cancer | 96          | IHC    | Positive vs negative  | 65 (67.7%) | Median 73 months | OS           | Multi    | Report    | 9          |
| Kim and Cha³⁰         | 2011 | Korea             | Oral cancer | 95          | IHC    | Positive vs negative  | 67 (70.5%) | > 5 years       | OS           | Multi    | Report    | 7          |
| Szarvas et al³⁰       | 2012 | Germany           | Urothelial carcinoma | 106 | IHC | Staining index >7 (0–9) | 17 (16.0%) | Median 15 months | OS CSS MFS   | Multi    | Report    | 7          |
| Simnikova et al³⁹     | 2008 | USA               | Urothelial carcinoma | 214 | IHC | Positive vs negative | 42 (19.6%) | Median 35 months | PFS DFS      | Multi    | Report    | 8          |
| Lee et al³¹           | 2013 | Multicenter       | Urothelial carcinoma | 622 | IHC | Positive vs negative | 76 (12.2%) | Median 27 months | OS CSS RFS   | Multi    | Report    | 9          |
| Niedworok et al³⁰     | 2015 | Germany           | Urothelial carcinoma | 26 | IHC | H-score > 100 (0–300) | 7 (26.9%) | Median 50 months | OS PFS       | Uni      | Report    | 7          |
| Bi et al⁴⁵            | 2016 | China             | Ovarian cancer | 73 | IHC | > 10% of cells stained | 46 (63.0%) | > 5 years       | OS           | Uni      | SC        | 7          |
| Kobel et al³⁶         | 2009 | British and Ireland | Ovarian cancer | 278 | IHC | > 5% of cells stained | 147 (52.9%) | > 4.6 years     | CSS          | Multi    | Report    | 8          |
| Hus et al³⁵           | 2015 | Taiwan            | Ovarian cancer | 140        | IHC    | The median value (IRS: 0–9) | NR | Median 39 months | PFS          | Multi    | Report    | 6          |
| Noske et al³⁷         | 2009 | Germany           | Ovarian cancer | 68          | IHC    | IRS >6 | 32 (47.1%) | Median 37 months | OS           | Uni      | SC        | 7          |
| Hu et al³⁴            | 2014 | China             | HCC         | 160         | IHC    | Staining score (2–7 vs 0–1) | 97 (60.6%) | Median 36 months | OS RFS       | Uni      | SC        | 8          |
| Wachter et al³⁶       | 2011 | Germany           | HCC         | 365         | IHC    | Staining group (2–3 vs 0–1) | 67 (18.4%) | Mean 23.3 months | OS           | Multi    | Report    | 7          |
| Chen et al³⁶          | 2013 | China             | HCC         | 92          | IHC    | Positive vs negative  | 65 (70.7%) | > 3 years       | OS           | Multi    | Report    | 7          |
| Yuan et al³⁸          | 2009 | Taiwan            | Colorectal cancer | 186 | IHC | > 50% of cells stained | 66 (35.5%) | Median >5 years  | OS           | Multi    | Report    | 8          |
| Li et al³⁹            | 2009 | China             | Colorectal cancer | 203 | IHC | Staining score (2–7 vs 0–1) | 132 (65.0%) | Median 61 months | OS DFS       | Multi    | Report    | 9          |
| Lochhead et al³²      | 2012 | USA               | Colorectal cancer | 671 | IHC | Intense or moderate vs weak or absent | 234 (34.2%) | Median 160 months | OS CSS       | Multi    | Report    | 8          |
| Lin et al³⁰           | 2013 | China             | Colorectal cancer | 186 | IHC | Positive vs negative  | 143 (76.9%) | > 2 years       | OS           | Multi    | Report    | 7          |
| Ilnenberg et al³³     | 2010 | Switzerland       | Prostate cancer | 425 | IHC | Positive vs negative | 354 (83.3%) | Median 63 months | RFS          | Uni      | Report    | 9          |
| Chromek et al³⁴       | 2011 | USA               | Prostate cancer | 232 | IHC | > 10% of cells stained | 42 (18.1%) | Median 69.8 months | RFS          | Multi    | Report    | 9          |
| Szarvas et al³⁰       | 2014 | Germany           | Prostate cancer | 124 | IHC | > 10% of cells stained | 30 (24.2%) | Median 155 months | OS CSS       | Uni      | Report    | 8          |
| Wang et al³²          | 2014 | China             | Pancreatic cancer | 50 | qPCR | Cutoff value based on the ROC curve | 30 (60.0%) | > 2 years       | OS           | Multi    | Report    | 7          |
| Schaeffer et al³¹     | 2010 | Canada            | Pancreatic cancer | 127 | IHC | IHC score >5 | 80 (63.0%) | Mean 13 months | OS           | Multi    | Report    | 8          |
analysis was performed to evaluate the prognostic role of IMP3 in 38 studies; and univariate analysis was conducted in the other 15 studies. Immunohistochemistry (IHC) staining and quantitative polymerase chain reaction (qPCR) were used to test the IMP3 expression in cancer tissues. Notably, the definition and cutoff of high IMP3 expression were heterogeneous among these studies. The majority of included studies used the percentage of positive staining cells (0%, 10%, 25%, or 50%) as the criteria, whereas in some other studies, staining scores with the percentage and intensity score were obtained as cutoff values for high IMP3 expression. The percentage of high expression in the cohort population varied in different cancer types and ranged from 6.5% to 83.3%. Quality score assessment suggested that the scores of enrolled studies ranged from 6 to 9, which were considered adequate for quantitative meta-analysis.

**Association of IMP3 with OS**

The association of IMP3 expression and OS was investigated in 40 studies containing 6,425 patients with different cancer types. A random-effect model was selected because of the evident interstudy heterogeneity ($I^2=59.1\%, P=0.005$). Combined analysis revealed that high IMP3 expression was associated with the worse OS of solid tumors (HR =2.08, 95% CI: 1.80–2.42, $P<0.001$, Figure 2). The effect of IMP3 expression on OS was further analyzed by tumor types, and the results are presented in Figure 3A. High IMP3 expression was significantly associated with poor OS in RCC (HR =2.80, 95% CI: 1.59–4.93, $P<0.001$), lung cancer (HR =1.87, 95% CI: 1.22–2.84, $P=0.004$), oral cancer (HR =1.66, 95% CI: 1.27–2.18, $P<0.001$), urothelial carcinoma (HR =1.92, 95% CI: 1.42–2.59, $P<0.001$), HCC (HR =2.25, 95% CI: 1.65–3.06, $P<0.001$), colorectal cancer (HR =1.52, 95% CI: 1.23–1.90, $P<0.001$), pancreatic cancer (HR =3.54, 95% CI: 2.06–6.09, $P<0.001$), gastric cancer (HR =2.67, 95% CI: 1.38–5.17, $P=0.003$), and ICC (HR =2.10, 95% CI: 1.52–2.92, $P<0.001$) but not in ovarian cancer (HR =1.05, 95% CI: 0.18–6.15, $P=0.957$).

To explore the source of heterogeneity, subgroup analysis and meta-regression were performed by the following stratification: patient ethnicity, study number, cutoff value, cancer stage, HR obtained method, and analysis style (Table 2). The results indicated that the combined HR estimates for OS in Caucasians and Asians were 2.08 (95% CI: 1.54–2.81, $P<0.001$) and 1.96 (95% CI: 1.73–2.22, $P<0.001$), respectively. Differences in the case number, cutoff value, cancer stage, HR obtained method, and analysis method did not influence the effect of IMP3 expression on the OS of solid tumors. Further meta-regression analysis revealed that cancer
stage is a potential significant contributor to heterogeneity ($P=0.017$), unlike other factors ($P>0.05$).

To assess the credibility of the pooled outcomes, we performed a sensitivity analysis through the sequential omission of individual studies. The results were not obviously influenced by any single study (Figure 3C). The publication bias of all included studies was evaluated using a vertical funnel plot, Begg’s, and Egger’s tests. However, the funnel plot in Figure 3B appears asymmetrical, and the Begg’s ($P=0.015$) and Egger’s tests ($P=0.002$) revealed existing evidence of publication bias, which may be attributed to only seven studies that reported negative results among all the enrolled studies.

### Association of IMP3 with CSS, DFS, RFS, PFs, and MFS

Ten studies that involved a total of 2,877 patients provided sufficient data for CSS analysis. No heterogeneity was observed among these studies ($I^2=13.3\%, P=0.158$). Thus, a fixed model was applied to pool the results. The combined
Figure 3 Subgroup analysis of OS stratified by tumor types, funnel plot of OS for publication bias, and sensitive analysis of OS.

Notes: (A) High IMP3 expression was significantly associated with poor OS in RCC, lung cancer, oral cancer, urothelial carcinoma, HCC, colorectal cancer, pancreatic cancer, gastric cancer, and ICC but not in ovarian cancer. (B) The funnel plot for OS was asymmetric, which indicated the probability of publication bias. (C) Sensitivity analysis by sequential omission of individual studies did not alter the significance, which confirmed the credibility of outcomes.

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; In, natural logarithm; IMP3, insulin-like growth factor II mRNA-binding protein 3; OS, overall survival; RCC, renal cell carcinoma; SE, standard error.
HR was 1.75 (95% CI, 1.50–2.05, P<0.001), indicating that high IMP3 expression was associated with worse CSS in the patients with solid tumors (Figure 4A). The subgroup analysis stratified by cancer types showed that high IMP3 expression significantly affected the RCC (HR =1.49, 95% CI: 1.11–2.01, P=0.008) and urothelial carcinoma (HR =2.17, 95% CI: 1.54–3.07, P<0.001). Further sensitivity analysis did not alter the significance of combined HR, which validated the outcome credibility. Eight studies that involved 979 patients reported HRs for DFS, and the effect of high IMP3 expression is presented in Figure 4B. A combined analysis showed that high IMP3 expression was associated with poor DFS in solid tumors (HR =3.30, 95% CI: 1.82–5.99, P<0.001).

Seven studies with 1,930 patients investigated the prognostic role of IMP3 expression in the RFS of solid tumors. Pooled results demonstrated that high IMP3 adversely influenced the RFS in patients with solid tumors (HR =2.11, 95% CI: 1.43–3.12, P<0.001, Figure 5A). For PFS, four studies with 457 patients were included in the analysis. A forest plot of study-specific HRs for PFS is presented in Figure 5B. The combined results indicated that high IMP3 expression was significantly associated with worse PFS in solid tumors (HR =2.18, 95% CI: 1.11–4.29, P=0.023). In addition, five studies, including 1,613 patients, focused on the influence of IMP3 on solid tumor metastasis. Meta-analysis of these studies suggested that IMP3 expression was also associated with poor MFS (HR =4.91, 95% CI: 2.05–11.73, P<0.001, Figure 5C).

### Discussion

Over the past decades, increasing correlative studies describe the elevated IMP3 expression in human cancers, and various functional in vitro or in vivo studies provide strong evidence indicating that this oncofetal protein serves an essential role in modulating tumor cell fate. As a molecular biomarker, IMP3 has attracted extensive attention and can be used to distinguish different prognoses, improve prediction accuracy, and better guide clinical decisions in different tumor types. Nevertheless, the relationship between IMP3 expression and oncological outcome remains controversial and requires a consensus. Consequently, we attempted to perform a systematic review of published relevant studies and conduct a meta-analysis to clarify the prognostic value of IMP3 expression in patients with solid tumors.

In the present research, given the inclusion criteria, 53 studies involving 8,937 patients were eligible, and the HRs of cumulative survival rates were summarized quantitatively by standard meta-analysis techniques. Our results suggested that high IMP3 expression was associated with worse OS of the solid tumors. Further subgroup analysis stratified by tumor type presented detailed results as follows. The negative prognostic effects of IMP3 on OS were specifically observed...
in RCC, lung cancer, oral cancer, urothelial carcinoma, HCC, colorectal cancer, pancreatic cancer, gastric cancer, and ICC. Besides OS, we also investigated other frequently used survival outcomes, including CSS, DFS, RFS, PFS, and MFS. Similar influences were found for high IMP3 expression regarding the abovementioned end points, which provide a relatively comprehensive assessment of the value of IMP3 acting as a prognostic biomarker in solid tumors.

Accumulated literature suggests that IMP3 contributes to various aspects of cancer by promoting target genes expression by either preventing mRNA decay or stimulating mRNA translation. IMP3 knockdown in vitro can significantly inhibit the translation of IGF2 mRNA resulting in the marked inhibition of cell proliferation. By using solid cancer transcriptome data, IMP3 was also found to be correlated with HMGA2 mRNA expression in a dose-dependent manner. Additional assay for elucidating the mechanism indicated that IMP3 may function as a cytoplasmic safe house and prevents miRNA-directed mRNA decay of HMGA2 during tumor progression. Another recent study identified IMP3 as capable of directly binding the mRNAs of cyclins D1, D3, and G1 in vivo and in vitro. The study also found that IMP3 can regulate the expression of these cyclins depending on their protein partner HNRNPM in six human cancer cell lines of different origins. In addition, IMP3 promotes tumor cell invasion and migration by targeting the epithelial–mesenchymal

Figure 4 Forest plot of studies evaluating HRs of high IMP3 expression in solid tumors for CSS and DFS.

Notes: (A) High IMP3 expression was associated with poor CSS in solid tumors (HR =1.75, 95% CI: 1.50–2.05, \( P < 0.001 \)). (B) High IMP3 expression was associated with poor DFS in solid tumors (HR =3.30, 95% CI: 1.82–5.99, \( P < 0.001 \)). Weights are from random-effects analysis.

Abbreviations: HR, hazard ratios; IMP3, insulin-like growth factor II mRNA-binding protein 3; OS, overall survival.
transition-associated molecular makers, including E-cadherin, Slug, and vimentin. Overall, IMP3 plays an essential and multifaceted role in human cancers. Hence, targeting IMP3 may serve as a potential strategy for anticancer therapy.

To our knowledge, our study is the first meta-analysis that comprehensively evaluated the association between IMP3 expression and prognosis in patients with solid tumors. However, several limitations of our study must...
be acknowledged. First, we only extracted summarized population-level data rather than individual subject data from published literature. Second, different cutoff values and definitions of high IMP3 expression were used in these included studies. Third, a marked study heterogeneity existed in some analyses. The subgroup analyses and meta-regression revealed that cancer stage might be a significant contributor to heterogeneity. Moreover, several potential factors such as cancer type, cutoff value, baseline characteristics (sample size, sex, age, and pathological subtype), and duration of follow-up may partially contribute to the heterogeneity. Among the enrolled studies, 10 works did not directly report the HRs. The calculated HRs, which were estimated using the methods of Tierney et al, might not be as dependable as those retrieved directly from the reported results. As such, the HRs inevitably introduced some statistical errors and may have influenced the pooled analysis. Furthermore, some studies only provided univariate analysis results, which may have introduced a bias toward overestimation of the prognostic value compared with multivariate analysis. The funnel plot and Egger’s test suggested the probability of publication bias because of fewer studies reporting negative results. However, the greater difficulty in publishing studies with insignificant results than those with significant results may be unavoidable. Finally, despite the well-recognized advantages of systematic review and meta-analysis, the results were based on the quality of the included studies. Thus, further high-quality studies with larger samples and a unified detection method are entailed to achieve a consensus on this matter.

**Conclusion**

The current evidence suggests that high IMP3 expression in tumor tissues is associated with adverse survival in various cancers. Hence, IMP3 might be a potential and promising biomarker that can be used to improve prognosis stratification and guide decision making in the treatment of solid tumors. Further well-designed studies are needed to confirm our findings and obtain more precise evaluations of the prognostic value of IMP3 in cancers.

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**Disclosure**

The authors report no conflicts of interest in this work.

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## Supplementary material

### Table S1 Checklist of PRISMA 2009

| Section/topic                          | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|----------------------------------------|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Title                                  |   | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                             | 1                 |
| Abstract Structured summary            | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2                 |
| Introduction                           |   | Describe the rationale for the review in the context of what is already known.                                                                                                                                   | 3                 |
| Objectives                             | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                       | 3,4               |
| Methods Protocol and registration      | 5 | Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.                                             | No                |
| Eligibility criteria                   | 6 | Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.                                | 4,5               |
| Information sources                    | 7 | Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                          | 4                 |
| Search                                 | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                | 4                 |
| Study selection                        | 9 | State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                          | 5                 |
| Data collection process                | 10| Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                         | 5                 |
| Data items                             | 11| List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.                                                                               | 5,6               |
| Risk of bias in individual studies     | 12| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                  | 5,6               |
| Summary measures                       | 13| State the principal summary measures (eg, risk ratio, difference in means).                                                                                                                                       | 5,6               |
| Synthesis of results                   | 14| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.                                                             | 6                 |
| Risk of bias across studies            | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).                                                                   | 6                 |
| Additional analyses                    | 16| Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                    | 6                 |
| Results Study selection                | 17| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                              | 7                 |
| Study characteristics                  | 18| For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.                                                                       | 7                 |
| Risk of bias within studies            | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                | 7–14              |
| Results of individual studies          | 20| For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group; (b) effect estimates and confidence intervals, ideally with a forest plot.       | 7–14              |

(Continued)
Table S1 (Continued)

| Section/topic       | #  | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Synthesis of results| 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                         | 7–14              |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see item 15).                                                                                                                                   | 7–14              |
| Additional analysis | 23 | Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                               | 7–14              |
| **Discussion**      |    |                                                                                                                                                                                                                   |                   |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).                                | 14,15             |
| Limitations         | 25 | Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).                                                      | 15,16             |
| Conclusions         | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                           | 17                |
| **Funding**         |    |                                                                                                                                                                                                                   | None              |
| Funding             | 27 | Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.                                                                    |                   |

**Notes:** Reproduced from Moher D, Liberati A, Tetzlaff J, et al, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med. 2009;6(7): e1000097.1

**Reference**

1. Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.