

# The prognostic and clinicopathological significance of RBM3 in the survival of patients with tumor

## A Prisma-compliant meta-analysis

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### Abstract

**Background:** RNA-binding motif protein 3 (RBM3) plays an important role in carcinogenesis and tumor progression. However, the prognostic role of RBM3 in human carcinomas remains controversial. Therefore, we took a meta-analysis to research the association between the overall survival of patients with cancer and the expression of RBM3.

**Methods:** Systematic literature research identified 17 potentially eligible studies comprising 4976 patients in ten different cancer types. Two researchers independently screened the content and quality of studies and extracted data. Correlations of RBM3 expression and survival were analyzed and the hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated.

**Results:** In the pooled analysis, overexpression of RBM3 was related to improved overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS) in patients with cancer having a pooled HR of 0.61 (HR = 0.61; 95% CI: 0.47–0.69), 0.57 (HR = 0.60; 95% CI: 0.50–0.71) and 0.54 (HR = 0.54; 95% CI: 0.38–0.78). Besides, subgroup analysis proved that overexpression of RBM3 was related to improved OS in colorectal cancer (HR = 0.61, 95% CI: 0.43–0.86), melanoma (HR = 0.32, 95% CI: 0.20–0.52), and gastric cancer (HR = 0.51, 95% CI: 0.35–0.73). However, subgroup analysis according to tumor type revealed that overexpression of RBM3 was not related to better OS in breast carcinoma (HR = 0.52, 95% CI: 0.17–0.61).

**Conclusions:** Our results indicated that RBM3 overexpression was significantly predictive of better prognosis in various human cancers. For certain tumors, overexpression RBM3 might be a marker of improved survival in humans with cancer, except for breast cancer.

**Abbreviations:** CI = confidence interval, DFS = disease-free survival, EMBASE = excerpta medica database, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, OS = overall survival, RBM3 = RNA-binding motif protein 3, RFS = recurrence-free survival.

**Keywords:** cancer, meta-analysis, prognostic, RBM3

## 1. Introduction

In worldwide, cancer remains the second leading reason for death and the capital cause of public health problems. By the American

Cancer Society researching and discovering, almost 1,735,350 new tumor cases and 609,640 tumor deaths were recorded to happen in 2018 in the United States.<sup>[1]</sup> In recent years, some articles<sup>[2–4]</sup> have proved that many biomarkers play a significant part in different kinds of tumors. However, only a little have been applied in clinical treatment and the overall survival for most tumors remains awful, and many research workers are searching novel tumor markers to increase the diagnostic and prognostic level in patients with cancer.<sup>[5]</sup> Therefore, we need to make the utmost efforts to find new prognostic biomarkers to assist their clinical treatment and diagnosis in tumors.

The RNA-binding motif protein 3 (RBM3) was first identified in a human fetal brain tissue cDNA library<sup>[6]</sup> which gene-encoded 2 alternatively spliced RNA transcripts and mapped to Xp11.23. According to special subgroups including single-stranded RNA binding proteins (SBPs), we have identified RNA-binding proteins with RNA-binding motifs (RBMs). By stimulating protein synthesis, anti-apoptosis, and proliferation, these SBPs are taken part in gene transcription and posttranslational regulation of RNA through the transformation of microRNA complexes.<sup>[7]</sup> According to previous researches, RBM3 binds to both RNA and DNA<sup>[8]</sup> which is participated in the preservation of DNA completeness, containing DNA-dependent replication, chromatin remodeling, DNA replication, regulation of RNA, and DNA integrity checkpoints.<sup>[9]</sup> Studies have shown that RBM3

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expression was found promoted in many different kinds of cancer tissues and maybe potential oncogene.<sup>[10]</sup> According to previous studies, overexpression of RBM3 has lately been related to an improved prognosis in some types of tumors, including breast cancer (BC),<sup>[11–13]</sup> ovarian cancer (OC),<sup>[14]</sup> urinary bladder cancer (UBC),<sup>[15]</sup> prostate cancer,<sup>[16,17]</sup> gastric cancer (GC),<sup>[18,19]</sup> lung cancer,<sup>[20]</sup> melanoma,<sup>[21,22]</sup> pancreatic cancer (PC),<sup>[23]</sup> and colorectal cancer (CRC).<sup>[24–26]</sup> However, a comprehensive meta-analysis demonstrated on the relationship between RBM3 expression and survival rate of different kinds of cancers has not been carried out yet. Therefore, we employed this meta-analysis to comprehensively study the prognostic value of RBM3.

## 2. Materials and methods

### 2.1. Search strategy

Articles published before July 9, 2019, were extracted from PubMed, the Web of Science, and Embase. We used the MeSH terms and keywords of “RBM3 or RNA-binding motif protein 3” and “neoplasms or cancer or tumor” and “prognosis or prognostic or overall survival or survival rate” in our searches. Meanwhile, we also looked through the reference lists of potential crux studies published in English to obtain additional relevant studies for data analysis.

### 2.2. Section criteria

We selected eligible studies based on the following standards:

1. statistics on the relationship between RBM3 expression and overall survival (OS) or disease-free survival (DFS) or recurrence-free survival (RFS) in patients with cancer;
2. either RBM3 protein or mRNAs were detected in cancer tissue;
3. researches separated patients into 2 groups based on RBM3 expression stage, regardless of the cut-off values; and
4. the studies reported HR with 95% confidence interval (CI) or we can calculate the HR with 95% CI by sufficient data.

The eliminated standards were

1. articles without enough statistics to calculate or evaluate HR with 95% CI or
2. letters, case reports, and reviews or
3. in vitro or animal studies or
4. sample size <20.

The searches also restricted to English language articles.

### 2.3. Data extraction

Two investigators (GY and XY) independently undertook the responsibility of extracting the statistics included in the articles which meet our criterion. A third investigator will judge disagreements when we have a difference of opinion. We also evaluate the quality of studies which satisfied our inclusion criteria by using the Newcastle–Ottawa scale (NOS).<sup>[27]</sup> The following information and statistics were recorded: the first authors name, country, year of publication, tumor kind, sample size, and outcome measures. As the same, HRs with 95% CI for OS, DFS or RFS were also extracted from the articles. However, when the articles just provided Kaplan–Meier curves, we will estimate the survival statistics by taking advantage of Engauge Digitizer version 4.1.<sup>[28]</sup>

### 2.4. Quality assessment

We assessed the above studies by NOS, and we judged the scores by pre-planned hypotheses, correlative details about the research design, statistical analysis methods, and patients characteristics. If studies with a score of more than 6, we will consider the studies as high quality.<sup>[29]</sup>

### 2.5. Statistical analysis

In our research, the prognostic worth of RBM3 expression in patients with various tumors was surveyed by calculated the HR between the positive expression of tissue RBM3 groups and negative expression of tissue RBM3 groups for OS, DFS, or RFS. We also measured the related 95% CI. Besides, we assessed the heterogeneity between articles with  $P$  value and  $I^2$ . If  $I^2 \geq 50\%$  or  $P \leq .10$ , we would believe that the studies existed obvious heterogeneity, and total HR was calculated by using a random-effect model. Oppositely, if heterogeneity of articles was not discovered ( $I^2 \leq 50\%$  and  $P \geq .10$ ), we will use a fixed-effects model. All data analyses were employed by utilized normalized statistical analyzing procedures offered in RevMan 5.3.

## 3. Results

### 3.1. Study characteristics

The particular searching process is revealed in Fig.1. After searching keywords on the Cochrane Library, Embase, PubMed, 1209 relative studies were identified. After we screened the title and abstract, 890 Records were excluded. Besides, 102 of the records HRs cannot be calculated. Of these, 20 studies were excluded because they failed to meet our eligibility criteria after screening the full texts. Finally, 17 studies were selected with a total of 4976 patients in our researches. As shown in Table 1, the sample size of these 17 studies ranged from 88 to 1473, with a mean of 284.5. Furthermore, these researches were published from 2009 to 2019 which from different countries, including 10 in Sweden, 3 in Germany, 3 in China and 2 in Korea. Among this included studies, 3 focused on BC, 3 on CRC, 2 on melanoma, 2 on GC, 1 on PC, 1 on hepatocellular carcinoma (HCC),<sup>[30]</sup> 1 on non-small-cell lung cancer (NSCLC), OC, testicular cancer (TC),<sup>[31]</sup> UBC, esophageal adenocarcinoma (EAC), and esophageal squamous cell cancer (ESCC).<sup>[32]</sup> The expression level of RBM3 was decided in many types of research with the same measurement way (immunohistochemistry) in most articles.

### 3.2. High RBM3 expression was associated with improved OS

Accumulative meta-analysis was carried out to evaluate the overexpression of RBM3 in the OS for tumor patients. In the pooled analysis of 17 eligible studies among 4976 patients with cancer, an obvious relationship was discovered between RBM3 expression and OS in patients with cancer (HR 0.61; 95% CI: 0.49–0.77;  $P < .00001$ ; Fig. 2). Such results may demonstrate that cancer patients with low RBM3 expression were associated with shorter overall survival. However, obvious heterogeneity was found among the qualified articles which met our standards ( $I^2 = 77\%$ ). Because of this, we used a random-effect.

Next, we performed a subgroup analysis to research whether the heterogeneity is due to different kinds of cancers. Tumors of the same types were combined to calculate a total of HR (Fig. 3).

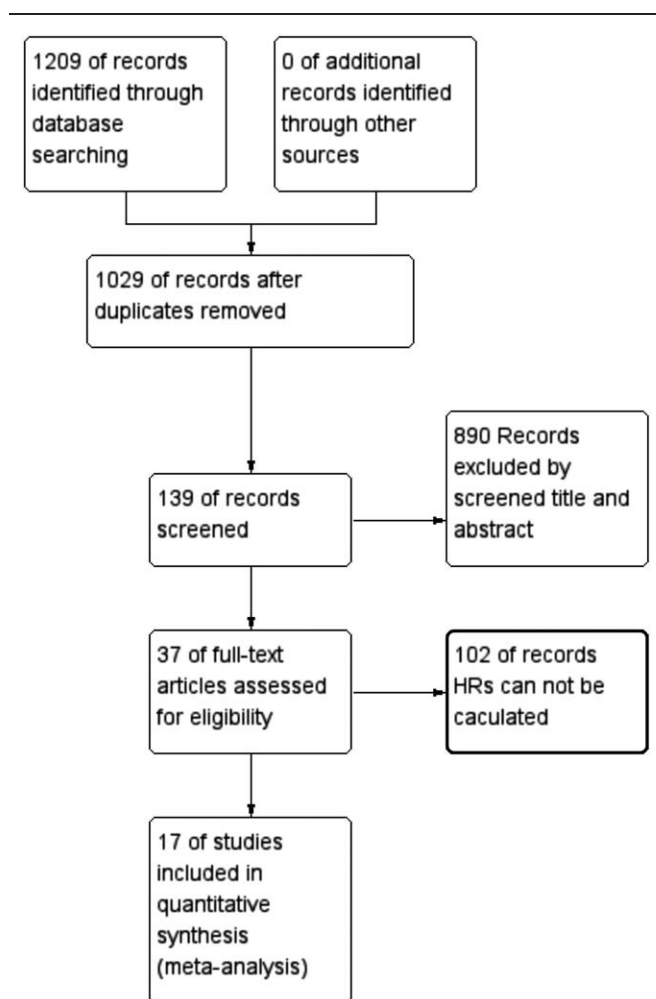


Figure 1. The flow chart of the selection process in our meta-analysis.

And, however, only studies about BC, GC, melanoma, and CRC were furtherly analyzed in the subgroup, for the reason that there was only 1 study on PC, HCC, OC, TC, UBC, ESCC, NSCLC, and EAC. Significant heterogeneity was found in breast cancer ( $I^2 = 84\%$ ). After reading through the full texts, we believed the sample sizes, different kinds of people and the number of studies were the reasons for that, and we need more studies to prove our conclusion. Totally, results showed that overexpression of RBM3 was associated with improved OS in colorectal cancer (HR = 0.61, 95% CI: 0.43–0.86,  $P = .005$ ), gastric cancer (HR = 0.51, 95% CI: 0.35–0.73,  $P = .0003$ ) and melanoma (HR = 0.32, 95% CI: 0.20–0.52,  $P < .00001$ ). However, subgroup analysis according to tumor kinds indicated that positive expression of RBM3 was not related to better OS in breast carcinoma (HR = 0.56, 95% CI: 0.22–1.42,  $P = .22$ ).

### 3.3. High RBM3 expression was associated with improved DFS and RFS.

We also made this Cumulative meta-analysis to find out the role of RBM3 from the eligible studies in DFS of 670 tumor patients (Fig.4) and the same in RFS of 1385 tumor patients (Fig. 5). There was no significant heterogeneity between DFS ( $I^2 = 0$ ) and RFS ( $I^2 = 31$ ). A fixed-effect model was then used, data analyses showed that positive RBM3 expression was related to improved DFS (HR = 0.54, 95% CI: 0.38–0.78) and RFS (HR = 0.60, 95% CI: 0.47–0.76) of patients.

### 3.4. Publication bias

We assessed the publication bias by visual and construction evaluation of funnel plot symmetry from Begg and Egger tests. According to this figure, we did not see obvious evidence of asymmetry in terms of the shape of this funnel plots. So, we considered that meta-analysis existed no obvious publication bias<sup>[33]</sup> (Fig.6).

Table 1 Main characteristics of 17 studies in the meta-analysis.

| Author         | Country | Year | Sample   | Sizes | OS                  | RFS              | DFS                 | NOS |
|----------------|---------|------|----------|-------|---------------------|------------------|---------------------|-----|
| Boman et al    | Sweden  | 2017 | UBC      | 272   | 1.85 (1.11–3.09)    | NM               | NM                  | 7   |
| Chen et al     | China   | 2019 | BC       | 103   | 1.49 (1.19–4.54)    | 2.22 (1.11–4.62) | NM                  | 7   |
| Dong et al     | China   | 2019 | HCC      | 151   | 0.57 (0.35–0.93)    | 1.75 (1.08–3.71) | NM                  | 8   |
| Ehlen et al    | Sweden  | 2010 | OC       | 154   | 0.62 (0.41–0.95)    | 0.61 (0.44–0.84) | NM                  | 8   |
| Grupp et al    | Germany | 2018 | EAC      | 359   | 0.81 (0.59–1.12)    | NM               | NM                  | 8   |
| Grupp et al    | Germany | 2018 | ESCC     | 254   | 0.93 (0.68–1.28)    | NM               | NM                  | 8   |
| Hjelm et al    | Sweden  | 2011 | CRC      | 271   | 0.55 (0.33–0.92)    | 0.61 (0.44–0.83) | NM                  | 8   |
| Jane et al     | Korea   | 2017 | CRC      | 94    | 0.73 (0.10–5.48)    | NM               | 0.61 (0.2–0.91)     | 8   |
| Jogi et al     | Sweden  | 2009 | BC       | 196   | 0.49 (0.30–0.79)    | 0.56 (0.36–0.90) | NM                  | 8   |
| Jonsson et al  | Sweden  | 2011 | melanoma | 215   | 0.33 (0.18–0.61)    | 0.50 (0.21–0.79) | NM                  | 7   |
| Jonsson et al  | Sweden  | 2014 | GC       | 120   | 0.51 (0.3–0.85)     | 0.33 (0.15–0.69) | NM                  | 7   |
| Kang et al     | Korea   | 2018 | BC       | 361   | 0.245 (0.133–0.451) | NM               | 0.199 (0.114–0.346) | 7   |
| Karnevi et al  | Sweden  | 2018 | PC       | 95    | 0.41 (0.21–0.80)    | 0.36 (0.19–0.69) | NM                  | 6   |
| Melling et al  | Germany | 2019 | NSCLC    | 467   | 0.541 (0.308–0.952) | NM               | NM                  | 7   |
| Melling et al  | Germany | 2016 | CRC      | 1473  | 0.93 (0.84–1.03)    | NM               | NM                  | 6   |
| Nodin et al    | Sweden  | 2012 | melanoma | 215   | 0.30 (0.14–0.71)    | NM               | 0.50 (0.27–0.91)    | 8   |
| Olofsson et al | Sweden  | 2015 | TC       | 88    | 0.27 (0.08–0.88)    | NM               | NM                  | 8   |
| Ye et al       | China   | 2017 | GC       | 88    | 0.504 (0.300–0.845) | NM               | NM                  | 7   |

BC = breast cancer, CI = confidence interval, CRC = colorectal cancer, DFS = disease-free survival, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell cancer, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, NM = not mention, NOS = Newcastle–Ottawa Scale, NSCLC = non-small-cell lung cancer, OC = ovarian cancer, OS = overall survival, PC = pancreatic cancer, RFS = recurrence-free survival, TC = testicular cancer, UBC = urinary bladder cancer.

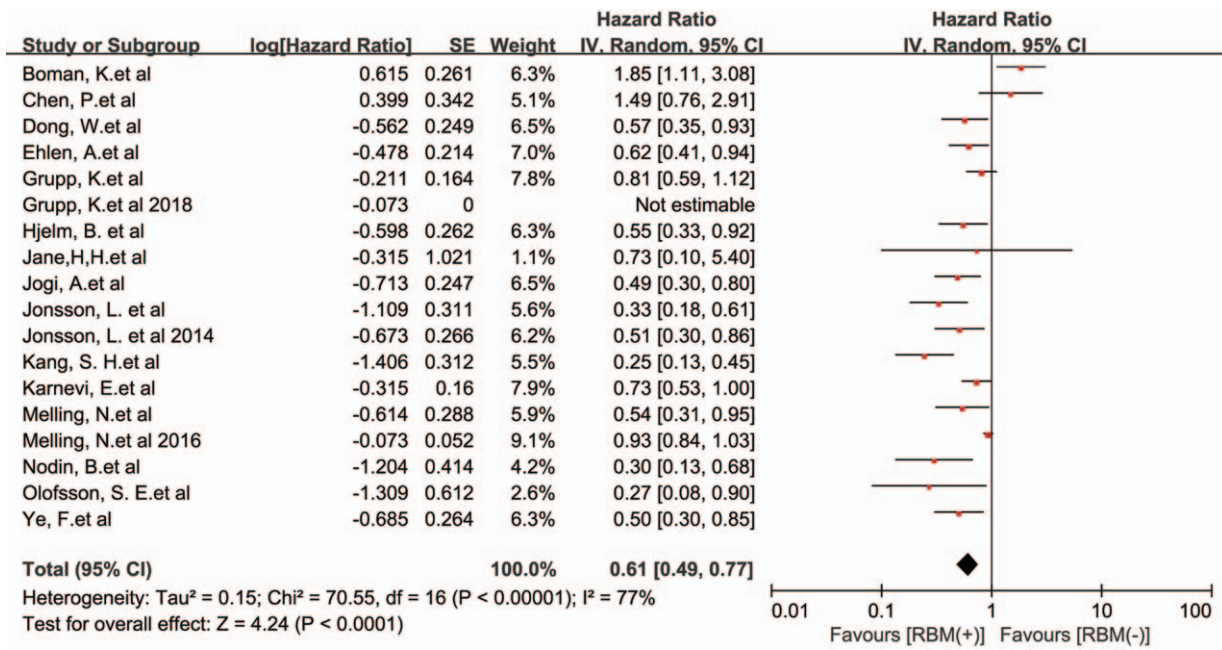


Figure 2. The correlation between RBM3 expression and overall survival in human cancer.

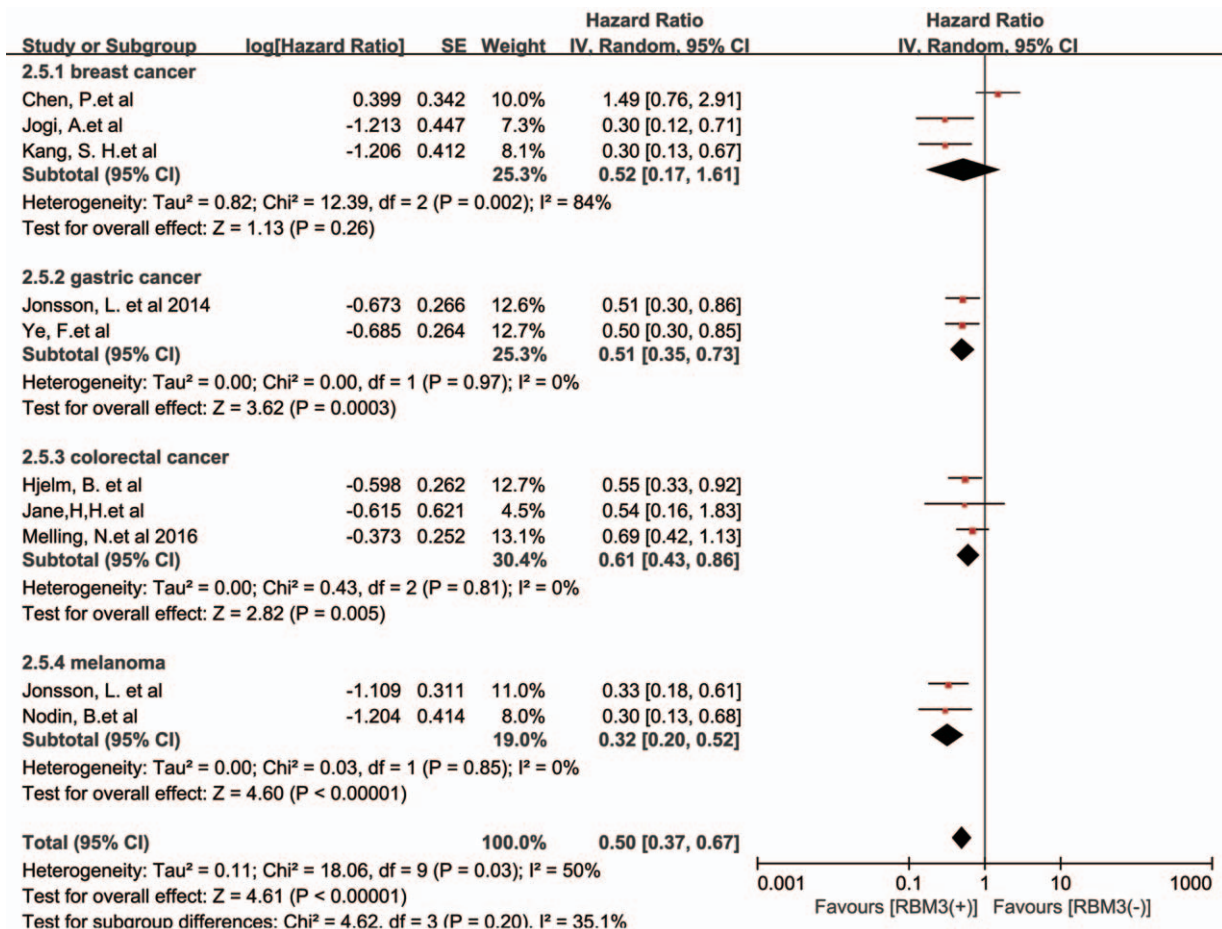


Figure 3. Forest plot demonstrating subgroup analysis of the relationship between RBM3 expression with OS in patients with breast cancer, melanoma, colorectal cancer or gastric cancer.

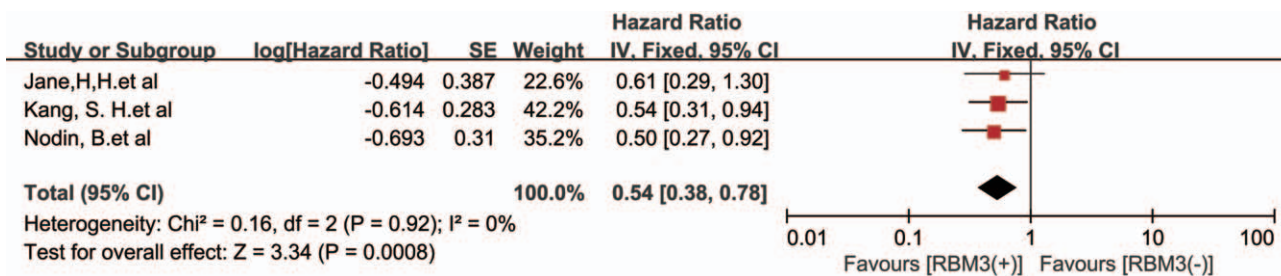


Figure 4. The correlation between RBM3 expression and DFS in human cancer.

#### 4. Discussion

Great progress has been achieved in tumor treatment and detection. In recent years, we have focused much attention on the identification of potential prognostic biomarkers in patients with tumors to improve efficacy and survival by taking advantage of this information.<sup>[34,35]</sup> The overall survival rate of patients with cancer remains relatively low for most kinds of tumors, and this is the reason why we demonstrated this meta-analysis. RNA-binding protein (RBP) plays an important role in the regulation of post-transcriptional gene expression, and it regulates cell function by binding to RNA.<sup>[36]</sup> Besides, RNA-binding motif protein 3 is a vital cold shock protein, and environmental stimulation such as hypothermia, hypoxia, and ischemia can increase its expression. In several kinds of tumor cells, upregulated RBM3 expression prevents apoptosis and promotes cell differentiation. Besides, previous researches on RBM3 expression in other cancers have often indicated a biological and clinical significance of RBM3 expression, but results varied between different kinds of cancer. Compared with normal tissue, there is an increase of RBM3 expression in gastric, prostate, and breast cancer. However, some studies reported a decreased RBM3 expression in non-cancerous relative to cancerous tissue in malignant melanoma, CRC, and UBC. We believed that these different observations may be a result of different interactions between RBM3 and other human gene products activated and expressed in individual organ kinds. In recent studies, researchers have confirmed that overexpression of RBM3 was related with improved prognosis in BC, CRC, melanoma, GC, HCC, NSCLC, OC, and TC, had no relations in EAC and ESCC, on the contrary,

had worse overall survival in UBC and PC. In addition, Boman et al reported that reduced RBM3 expression related with a significantly shorter time to cancer progression.<sup>[15]</sup> Also, Chen et al reported that RBM3 regulated ARPC2 in a positive manner and the regulatory effects were monitored by post-transcriptional 3'UTR binding which mediated the promoting key role of RBM3 in the metastasis and proliferation of BC cells.<sup>[11]</sup> Dong et al revealed that SCD-circRNA 2 may play a role of a downstream target molecule of RBM3 which affects HCC progression.<sup>[30]</sup> Furthermore, Ehlen et al reported that decreased RBM3 expression may reduce platinum sensitivity in ovarian tumor cells.<sup>[14]</sup> Jonsson et al also reported RBM3 expression was lost during development of the melanoma and was an independent biomarker of a prolonged overall survival in patients.<sup>[21]</sup> In our meta-analysis, the prognostic value and clinicopathologic significance of RBM3 in patients with cancer were investigated. By researching genes particularly associated with overall survival and organ differentiation would help us comprehend the procession of tumorigenesis. Besides, this meta-analysis would offer a basis for study into the treatment worth of RBM3 in tumors.

Four thousand nine hundred seventy six tumor patients from 17 qualified articles were pooled and analyzed in our meta-analysis. Based on the front inclusion and exclusion standard, 12 cancer kinds in 17 qualified articles, containing 9 in Sweden, 3 in Germany, 3 in China, and 2 in Korea had accorded with our standards. However, the conclusions might be just fitted for the European population. Therefore, articles from other regions were required to decide whether the conclusions were suitable for all

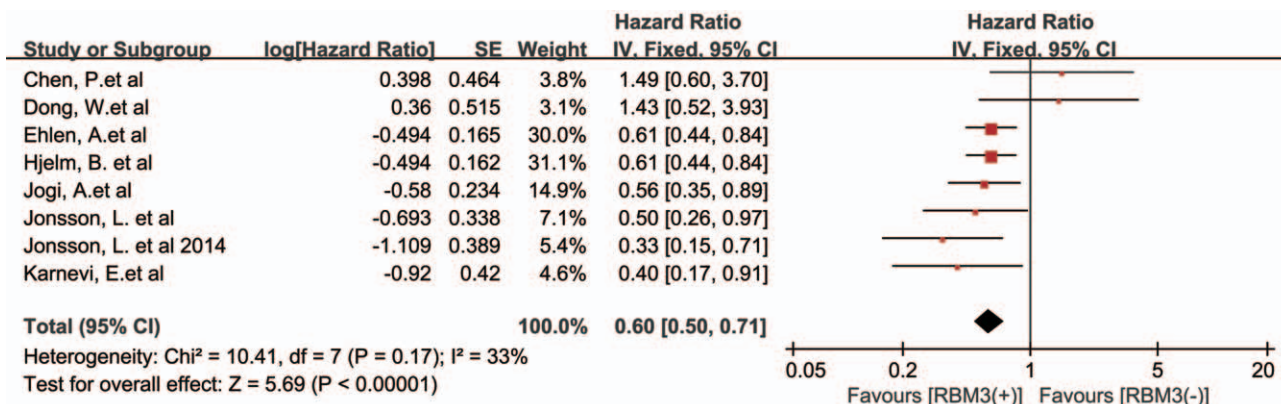
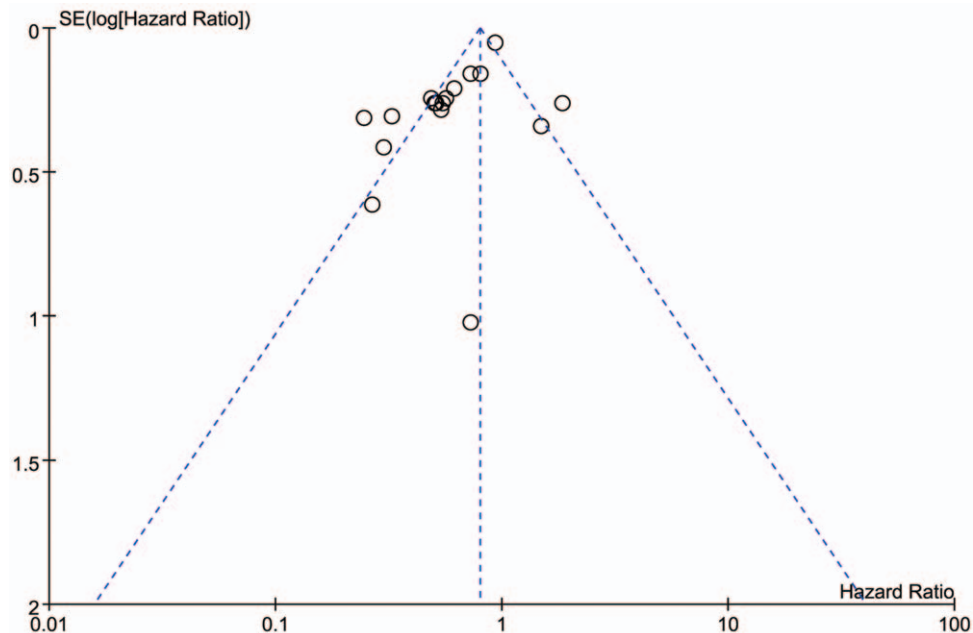


Figure 5. The correlation between RBM3 expression and RFS in human cancer.



**Figure 6.** Begg funnel plots for the studies involved in the meta-analysis. loghr = logarithm of hazard ratios; s.e.= standard err.

regions worldwide. A random or fixed-effects model was taken advantage of in this meta-analysis according to the heterogeneity examination. The combined HR revealed that overexpression of RBM3 was related to the improved prognosis of patients with different kinds of cancer. Subgroup analysis of studies including 2 studies of patients with melanoma, GC, and CRC supported this conclusion. On the contrary, there was no adequate evidence that increased expression of RBM3 was to longer OS time in patients with BC. In terms of RFS and DFS, we found that over RBM3 expression was correlated with improved DFS and RFS. Due to the limited number of studies and sample sizes for each cancer site, these conclusions required more and more prospective articles for certification.

However, there were several limitations to our meta-analysis. First, there was obvious evidence of heterogeneity; second, some survival statistics based on the calculation of Engauge Digitizer should be taken into account with carefulness, and we only included English language articles. Third, only 17 studies including 4976 patients participated in this meta-analysis and the number of researches applied in the subgroup analyses on DFS, RFS, and Specific types of tumors was not enough, which held back us from offering more certification to approve the observed tumor relationship. Fourth, it is nonuniform about the definition of cut-off values for the expression of RBM3 in different researches. Therefore, more multicenter, homogeneity, and large sample studies were needed to achieve more accurate conclusions.

## 5. Conclusion

As a conclusion, overexpression of tissue RBM3 may have an intimate relationship with improved OS, DFS, and RFS in patients with cancer according to the evident statistical significance. For some types of cancers, RBM3 might be a prognostic marker of better prognosis in patients with GC, CRC,

and melanoma, except for BC. Totally, overexpression of RBM3 might be applied as a potential prognostic factor for early diagnosis of better survival and may aid as a novel biomarker for tumor therapy in the future.

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## Author contribution

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