Clinicopathological and prognostic significance of Fusobacterium nucleatum infection in colorectal cancer: a meta-analysis

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Abstract

Background: Accumulating evidences about the association between Fusobacterium nucleatum (F. nucleatum) and colorectal cancer (CRC) has been reported in various studies. However, the definite relationship between abundance of F. nucleatum with clinical characteristics and prognosis of CRC is still controversial.

Methods: PubMed, Embase and Web of Science were searched for relevant articles up to April 7, 2020. Outcomes of interest included clinical characteristics, molecular characteristic and survival analysis. HR (OR), odds ratios (OR) and 95% confidence interval (CI) were calculated to explore the prognostic value and relationship of clinical characteristics of Fusobacterium nucleatum in CRC.

Results: A total of 3626 patients with CRC from 13 eligible studies were included. High abundance of F. nucleatum was associated with worse prognosis on overall survival (OS) (HR= 1.40, P < 0.0001), disease-free survival (DFS) (HR = 1.71, *P* = 0.0002) and cancer-specific survival (OR= 1.93, *P* <0.0001). In addition, F. nucleatum abundance was related with T (T3-T4) stage(OR = 2.20, *P* < 0.00001), M (M1) stage (OR = 2.11, *P* = 0.005), poor tumor differentation(OR = 1.83, *P* =0.02), microsatellite instability (MSI) -high (OR = 2.53, *P* = 0.0003) and KRAS mutation (OR =1.27, *P*=0.05).

Conclusion: The present evidences revealed that high abundance of F. nucleatum is inclined to indicate worse prognosis and is associated with tumor growth, distant

Impact: This study highlights the risk factor of F. nucleatum for worse prognosis of CRC.

Background

Colorectal cancer (CRC) is the third frequent malignant tumor with 1.85 million of new cases per year around the world base on the statistics in 2019 of the International Agency for Research on Cancer (IARC) of the World Health Association (WHO).[1] Although comprehensive treatment such as surgery, chemoradiotherapy, anti-angiogenesis and immunotherapy had been made a great progress for the treatment of CRC, the 5-year survival rate of CRC patients with distant metastasis is only 10% -20%.[2] Therefore, to discover risk factors related to the prognosis is important to improving the survival of CRC patients. Previous studies had been reported that genetic mutations, epigenetic changes, chronic inflammation, diet, and lifestyle are important factors for the survival of CRC patients[2]. Recently, some studies found that intestinal microecological balance is also closely related to the prognosis of CRC.[3] A study of Johnson. C et al showed that colonic mucosal biofilms produced by intestinal flora may affect the development and progression of cancer as regulator of cellular proliferation and colon cancer growth.[4] However, the role of gut microbiota in CRC is still not entirely clear as its complexity.

Fusobacterium nucleatum (F. nucleatum) as a kind of gram-negative bacilli in gastrointestinal tract has ability to mediate important biofilm tissue behaviors and interactions with host cells through the expression of numerous adhesins.[5] Previous studies have proved that it may has a close relationship

with occurrence and metastasis of colorectal cancer in many studies.[5–7] Former clinical cohort studies demonstrated that high abundance of F. nucleatum could be a prognostic biomarker of CRC, and associated with higher colorectal cancer-specific mortality. [8]On the contrary, some of them indicated that there is no significant correlation between the degree of F. nucleatum enrichment and the prognosis of CRC, especially in the analysis of clinical survival rate.[9] Collectively, the relationship of F. nucleatum infection and prognosis and clinical characteristics of CRC is still controversial.

In the light of the controversial statements mentioned above, we conducted this meta-analysis with an integrated large sample size to clear the role of F. nucleatum the prognostic value of patients with CRC.

Methods

Data sources

We searched PubMed, Embase and Web of Science for relevant studies published up to April 7, 2020. According to the standard meta-analysis guidelines, relevant articles were searched and accessed through PubMed, Web of Science, Medline, and Embase, using MeSH. Key terms including the following: “Fusobacterium nucleatum”, “Fusobacterium spp”, “Fn”, “Colorectal Neoplasm(s)”, “Colorectal Tumor(s)”, “Colorectal Carcinoma(s)”, “Colorectal Cancer(s)”, “prognosis”, “Prognoses” and “Prognostic Factor(s)”.

Inclusion And Exclusion Criteria

In this meta-analysis, studies fulfilling the following criteria were eligible for inclusion: (1) the articles should be original articles; (2) All included studies were controlled clinical studies of CRC patients with complete data; (3) the diagnosis of CRC should be based on histology; (4) subjects of studies were human, and the experimental samples were tumor tissues and surrounding tissues after surgical resection; (5) in the included studies, DNA content of F.nucleatum in tissues was detected by quantitative PCR or 16sRNA sequencing or other detection methods and cases with detectable fusobacteria DNA were divided into low abundance and high abundance for study according to the median cut-off point amount of F.nucleatum DNA. The review articles, meeting minutes, letters and only abstracts were excluded in this meta-analysis to ensure that original data is obtained. For studies with the same research team or with overlapping subjects, we selected the articles with the most comprehensive data.

Data Extraction

Data for each study were extracted independently by two independent reviewers, H.F and J. P, and verified by predefined standards. When there were disagreements between the two reviewers, it is decided by the third reviewer. The information and data of the included articles were collected as follow: the first author’s name, the year of publication, patient ethnicity, date of birth, sample size for different types (F. nucleatum -high/ F. nucleatum -low), sample type, diagnostic techniques of F. nucleatum, the tumor-node-metastasis

(TNM) stage, tumor-associated genes type (KRAS mutation and BRAF mutation) and microsatellite instability (MSI), survival analysis and follow-up time. The survival data were directly applied if an article stated the detailed ORs and 95% CIs for survival; otherwise, the Engauge Digitizer 4.1 (http://digitizer.sourceforge.net/) was used to extract survival data from Kaplan-Meier curves. [10] In studies that reported a univariate and a multivariate analysis for the same comparison, we only used the latter. Any discrepancies were discussed and resolved by consensus. The articles was graded on the Newcastle-Ottawa scale (NOS) to ensure the quality of the included studies.[10] Including domains were as follow: Adequacy of case definition, Number of cases, Representativeness of the cases, Ascertainment of exposure, Ascertainment of detection method, Ascertainment of cutoff, Assessment of outcome, and Adequate follow-up. A higher score indicates better methodological quality.

Statistical Analysis

The meta-analysis was performed by means of Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). As for dichotomous variables, the odds ratios (OR) were calculated, reporting 95% CI. Survival outcomes were summarized by adopting the generic inverse variance method. Overall survival (OS) was defined as the time from diagnosis until death. Disease-free survival (DFS) was defined as the interval between the initial primary diagnosis of CRC and the first relapse or death. Hazard ratio (HR) and 95% CI were calculated to assess the association between high abundance of F. nucleatum and survival. The results were aggregated and analyzed by utilizing a fixed effects model with $I^2 < 50\%$. If the I^2 statistic was higher than 50%, the random-effects analysis would be performed. The pooled effects were determined by conducting a Z test, and the statistical significance was defined as the two-sided $P < 0.05$.

Results

Flow Diagram of the Studies Retrieved for the Review

All 77 articles were identified through electronic databased searching after filtration. Among them, 15 articles were duplicated, 27 articles were excluded because of unmatched titles and abstracts, 22 articles were excluded from reading full texts (because of inappropriate objects and incomplete data). The final 13 articles[8–9, 11–21] included 3,690 CRC patients were selected to further meta-analysis. Figure 1 reveals the flowchart of study selection.

Baseline Characteristics of Included Studies

Table 1 summarizes the main characteristics of the eligible 13 studies. The analysis included 3,690 patients, ranging includes included 8 countries, from North America, Asia and Europe. All the specimens were tumor tissues after surgical resection. The most commonly used test method for F.nucleatum was quantitative polymerase chain reaction(qPCR),[8, 12–15, 18–21] besides, three studies[9, 11, 16] used the 16S

ribosomal RNA(16sRNA) and Yuko Yamaoka used droplet digital PCR.[17] All patients described in the retrieved articles were divided into two groups based on high or low expression of F.nucleatum DNA.

Association Between F.nucleatum Abundance And Prognosis Of Crc Patients

As the role of F.nucleatum in the prognosis of CRC patients is still controversial, we firstly analyzed the relationship between F.nucleatum abundance and prognosis of patients with CRC. Nine studies[8–9, 12, 15–17, 19–21] reporting on a total of 2158 patients were selected for analysis of the association between abundance of F.nucleatum and OS.The fixed-effects model was adopted as a result of low heterogeneity. As shown in Fig. 2A, high abundance associated with worse OS in the patient with CRC (HR = 1.40, 95% CI: 1.40–1.63, $P < 0.0001$), without significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.80$).

Moreover, data from five articles[9, 14, 16, 18, 20] for a total of 1270 patients were selected for analysis of the association between the abundance of F.nucleatum and DFS. The fixed-effects model was applied as a result of low heterogeneity ($I^2 = 0\%$, $P = 0.96$). Our results demonstrated that the CRC patients with high abundance of F.nucleatum associated worse DFS than those with low abundance of F.nucleatum (HR = 1.71, 95% CI: 1.29–2.26, $P = 0.0002$)(Fig. 2B).

Last but not least, a total of 1498 patients in three studies[8, 18, 21] were included to examine the relationship between the abundance of F.nucleatum and cancer-specific survival (CSS). In this analysis, F.nucleatum enrichment was significantly associated with poor CSS (HR = 1.93, 95% CI: 1.42–2.62 $P < 0.0001$) through the application of the fixed-effects model, with low heterogeneity ($I^2 = 0\%$, $P = 0.69$). (Fig. 2C)

Association Between high abundance of F.nucleatum and CRC Clinical Characteristics

As listed in Table 2, data from eleven articles[8, 11–19, 21] for a total of 3413 patients were selected for analysis of the association between the abundance of F.nucleatum and primary tumor site in a random-effects model ($I^2 = 60\%$, $P = 0.005$). The result suggested that there is no significance evidence proving the correlation between F.nucleatum infection and tumor site (OR = 1.26, 95% CI: 0.91–1.75, $P = 0.17$) (supplemental Fig. 1A).

A total of 3758 patients in nine studies[8, 11–17, 21] were included to examine the relationship between the abundance of F.nucleatum and TNM stage (supplemental Fig. 1B). The F.nucleatum abundance was not associate with the overall TNM stage of CRC (OR = 1.20, 95% CI: 0.96–1.51, $P = 0.11$), with low heterogeneity ($I^2 = 25\%$, p = 0.22). However, high abundance of F.nucleatum was correlated with higher T (T3-T4) (OR = 2.20, 95% CI: 1.66–2.91, $P < 0.00001$) and M (M1) (OR = 2.11, 95% CI: 1.25–3.56, $P = 0.005$)

stage respectively, without heterogeneity (I^2 = 0%). And eight studies reporting on a total of 1445 patients revealed that F.nucleatum enrichment had no obvious correlation with N stage (OR = 1.27, 95% CI: 0.98–1.64, P = 0.07), with low heterogeneity (I^2 = 37%) (supplemental Fig. 1C-E). Therefore, our result reveal that high abundance of F.nucleatum was associate with increasing of tumor size and distant metastasis in the CRC.

Furthermore, eight studies[8, 11, 15–19, 21] reporting the association between the abundance of F.nuleatum and tumor differentiation with a total of 2118 patients were selected to analyze (supplemental Fig. 1F). As shown in Table 2, F.nuleatum enrichment was significantly associated with poor tumor differentiation (OR = 1.83, 95% CI: 1.11–3.03, P = 0.02) in CRC patient, with high heterogeneity (I^2 = 60%).

Association Between high abundance of F.nucleatum and molecular characteristics in CRC

In order to further reveal the association between F.nucleatum infection and CRC progression, we analyzed the association between F.nucleatum enrichment and tumor-specific molecular characteristics. As shown in Table 3, our data from six studies[8, 11–14, 21] demonstrated that high abundance of F.nucleatum were significantly associated with MSI-high type CRC (OR = 2.53, 95% CI: 1.53–4.20, P = 0.0003), although with high heterogeneity (I^2 = 83%, P < 0.0001) (supplemental Fig. 2A). Interesting, the correlation between F.nucleatum enrichment and KRAS mutation was also found in fixed-effects model with low heterogeneity(I^2 = 28%, p = 0.23) in six studies. [8,11–14, 17] The OR was 1.27 with a 95% CI of 1.00–1.61(P = 0.05) (supplemental Fig. 2B).

Moreover, six studies[8, 11–14, 21] reporting on a total of 2499 patients were selected for analysis of the association between the abundance of F.nucleatum and BRAF mutation. Our result demonstrated that high abundance of F.nucleatum were not associate with BRAF mutation in CRC patient (OR = 1.93, 95% CI: 0.91–4.11, P = 0.09) (supplemental Fig. 2C). In addition, our pool result with three studies[8, 17, 21] found that F.nucleatum enrichment in CRC tissue has no correlation with MLH1 hypermethylation (OR = 0.78, 95% CI: 0.06–9.93, P = 0.84) (supplemental Fig. 2D). At last, a total of 1603 patients in three studies[8, 12, 13] were selected for analysis of the association between F.nucleatum enrichment and PIK3CA mutation through fixed-effect model, and there was no correlation between and PIK3CA mutation in CRC (OR = 1.21, 95% CI: 0.74–1.97, P = 0.45)(supplemental Fig. 2E).

Sensitivity Analysis

To evaluate the impact of a single study on the overall meta-analysis, included studies detecting F.nucleatum by qPCR or qrT-PCR were selected to perform sensitivity analysis (Table 4). The results of the sensitivity analysis are summarized in Table 4. The analysis of the studies using qPCR or qrT-PCR showed similar results to those of all studies together, including the relationship between F.nucleatum and Tumor side, TNM Stage, T stage, N stage, KRAS mutation, OS and DFS in CRC.

Risk Of Bias

The funnel plot were performed to assess publication bias. As shown in Fig. 3, the shape of funnel plots of main result was roughly symmetrical, without obvious evidence of asymmetry. The funnel plots for main outcomes, including OS, DFS and CSS, demonstrated no evidence of publication bias in our study.

Discussion

This meta-analysis demonstrates that high abundance of F.nucleatum is closely related to the poor prognosis of patient with CRC, including OS, DFS and CSS. Moreover, the correlation between the clinicopathological features of CRC, such as tumor site, clinical stage and tumor differentiation, also were found in our meta-analysis. In addtion, we also analyzed the correlation between the abundance of F.nucleatum and molecular characteristics of CRC such as MSI and mutation of KRAS, BRAF and PIK2CA, as well as MLH1 hypermethylation. Interesting, our result also further confimed that high abundance of F.nucleatum were significantly associated with MSI-high type and KRAS mutation of CRC. Although previous meta-analysis had reported the carcinogenesis and diagnostic value of F. nucleatum for CRC, as well as the prognosis of F. nucleatum in CRC with very little literatures. [22,23] To our best knowledge, this is the first meta-analysis to demonstrated the role of F.nucleatum in clinical and molecular characteristics of CRC, and the most comprehensive meta-analysis to clarify the prognostic role of F.nucleatum in CRC.

Firstly, our meta-analysis clarify the association between F. nucleatum abundance and the prognosis of CRC, including OS, DFS and CSS. Our result cleared that high abundance of F. nucleatum is correlate with poor OS of CRC patients. This result is similar with the previous study, [23] which report that F. nucleatum positivity in tumor tissue was associated with poorer OS in CRC patient. However, they found F. nucleatum positivity was not associated with the DFS and CSS in CRC patient. In our study, more studies were included to demonstrate that F. nucleatum abundance was associated with poorer DFS and CSS in CRC, and without heterogeneity between the studies. Many evidences had shown that F. nucleatum is associated with CRC development. As a conditional pathogen. F. nucleatum has a high detection rate in metastatic CRC lesions. [24]

Moreover, this is the first meta-analysis demonstrated that a higher abundance of F. nucleatum in CRC tissue was not associated with tumor side. Although, previous study[25] reported that the proportion of F. nucleatum-high colorectal cancers gradually increases from rectum to cecum. However, another study [14] reported that high F. nucleatum status had no correlation of tumor sidedness in CRC patients. Therefore, as F. nucleatum is a critical cancer-promoting factor, our result provided a more convincing evidence to confirm the relationship F. nucleatum status and tumor sidedness.

In addition, we also firstly verify the relationship between F. nucleatum and clinical stage of CRC base on the pool results. Interesting, our result revealed that F. nucleatum had no correlation with the overall TNM stage, but high abundance of F. nucleatum associated with higher T stage and M stage of CRC. This means that F. nucleatum promoting CRC proliferation and distant metastasis. Several studies had initially

reveal underlying mechanisms that FadA protein, a abhesion molecules of F. nucleatum, which binds to wnt7b E-cadherin on CRC cells and promotes F. nucleatum adhesion and invasion of host epithelial cells. Then F. nucleatum activates β-catenin signaling that regulating expression of related oncogenes and promotes colorectal cancer cells proliferation. [26] Moreover, F. nucleatum promotes the expression of several cytokines such as IL-6, IL-8 and IL-18, and lead to a proinflammatory microenvironment in CRC which accelerates CRC growth and metastasis. [26] Although our meta-analysis result showed a marginal association of F. nucleatum abundance with the higher N stage of CRC, therefore more evidence should clarify the role of F. nucleatum in lymphatic metastasis of CRC. At last, we also firstly found high abundance of F. nucleatum associated with poor differentiation of CRC via meta-analysis. This result also confirmed the F. nucleatum not only is associated with carcinogenesis, but also poor tumor differentiation of CRC.

Colorectal cancers develop through the accumulation of genetic and epigenetic alterations, influenced by microbial and other environmental exposures and host responses to the exposures. In the current study, high abundance level of F. nucleatum infection was related with key tumor molecular features of colorectal cancer, including MSI-high and KRAS mutation, which have been associated with clinical outcome in advanced colorectal cancer. The present data indicate a significant correlation between F. nucleatum enrichment and MSI-high from six studies of 2520 patients. MSI status was been commonly proved as a critical predictor for prognosis, response to chemotherapy or immunotherapy in CRC patients. [27–29] And prevous study reported the relationship of F. nucleatum with immune response to CRC by different MSI status, [30] which suggesting that F. nucleatum abundance correlated with MSI status and regulates antitumor immune response in CRC. Moreover, KRAS mutation also is an important molecular feature for chemotherapy resistance in CRC, [31] and F. nucleatum was abundant in colorectal cancer tissues also will cause chemoresistance. [32] Therefore, our result further confirmed this correlation which imply F. nucleatum is another underlying biomarker for response of immunotherapy and chemotherapy. At last, we firstly conducted a meta-analysis that proving no significant association with high abundance of F. nucleatum with mutation of BRAF and PIK2CA, as well as MLH1 hypermethylation in the CRC tissue. These results agree with findings from previous studies conducted in single populations, suggesting a role of F. nucleatum mainly with specific mutations in CRC. A more in-depth study of the association between the F. nucleatum and other mutations of CRC, such as TP53, AKT1, PTEN and so on, can reveal more biological roles of F. nucleatum in CRC.

Our meta-analysis inevitably had some limitations as following. Firstly, the number of the included studies was relatively small and the included studies were only English researches, which might bring some publication bias. Secondly, although sensitivity analysis had been conducted and further confirmed our results in our study. However, most of included studies were detected F. nucleatum abundance by qPCR, but some studies were detected by 16sRNA sequencing, the different method and cut-off value may cause some heterogeneity in some results. At last, there were some included studies do not reported HRs and 95% CIs in the prognostic outcomes. We attempted to extract survival data from Kaplan-Meier

curves according to the previous reported method. [10] This may impact the precision of the prognostic outcomes of F. nucleatum in CRC.

Despite these shortcomings, there is sufficient evidence to suggest that CRC with high-abundance F. nucleatum are at high risk of poor prognosis, including OS, DFS and CSS. And our result also suggest high-abundance F. nucleatum are correlate with tumor growth, distant metastasis, poor differentation, MSI-high and KRAS mutation in CRC. Future research on the relationship between F. nucleatum and more clinical and molecular characteristics in CRC should be assessed. In addition, understanding more mechanism of F. nucleatum in regulating progress of CRC, and whether antibiotic therapy base on F. nucleatum will help to prolong the prognosis of patient with CRC, will facilitate identification of more treatment strategies in CRC.

Abbreviations

F. nucleatum: Fusobacterium. nucleatum

CRC: colorectal cancer

qPCR: quantitative polymerase chain reaction

16sRNA: 16S ribosomal RNA sequencing,

qrT-PCR: quantitative reverse transcription polymerase chain reaction

OS: overall survival

DFS: disease-free survival

CSS: cancer-specific survival

MSI: microsatellite instability

KRAS: k-ras gene mutation

BRAF: b-raf gene mutation

MLH1: MLH1 hypermethylation

PIK2CA: PIK3CA gene mutation.

Declarations

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Not applicable.

Authors' contributions

SH participated in data analysis and wrote the manuscript. HJ and JP reviewed the manuscript. all Authors read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent to publish the clinical data was obtained from the patient before the initiation of the study.

Data availability

The data and materials are available upon request.

Conflict of interest

The authors declare that they have no competing interests.

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Tables

Due to technical limitations the Tables are available as downloads in the Supplementary Files.

Table 1. Characteristics of the included studies

Table 2. Association between high F.nuleatum abundance and Clinical characteristics of patients with CRC

Table 3. Association between high F.nuleatum abundance and molecular characteristic of patients

with CRC

Table 4. Sensitivity analysis of studies evaluated F.nuleatum on clinicopathological characteristics of

CRC

Figures

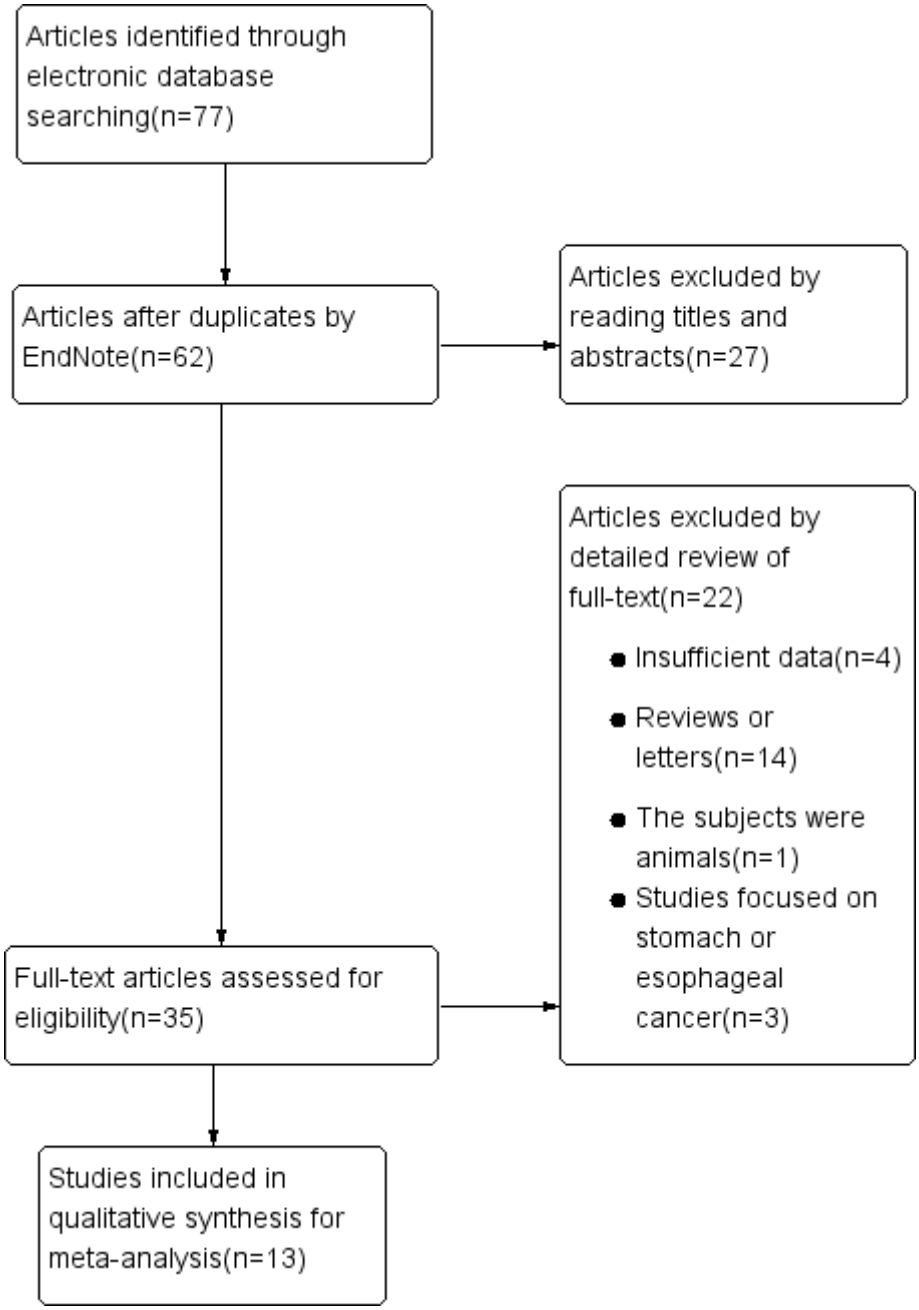

Figure 1

Flow diagram of study selection process.

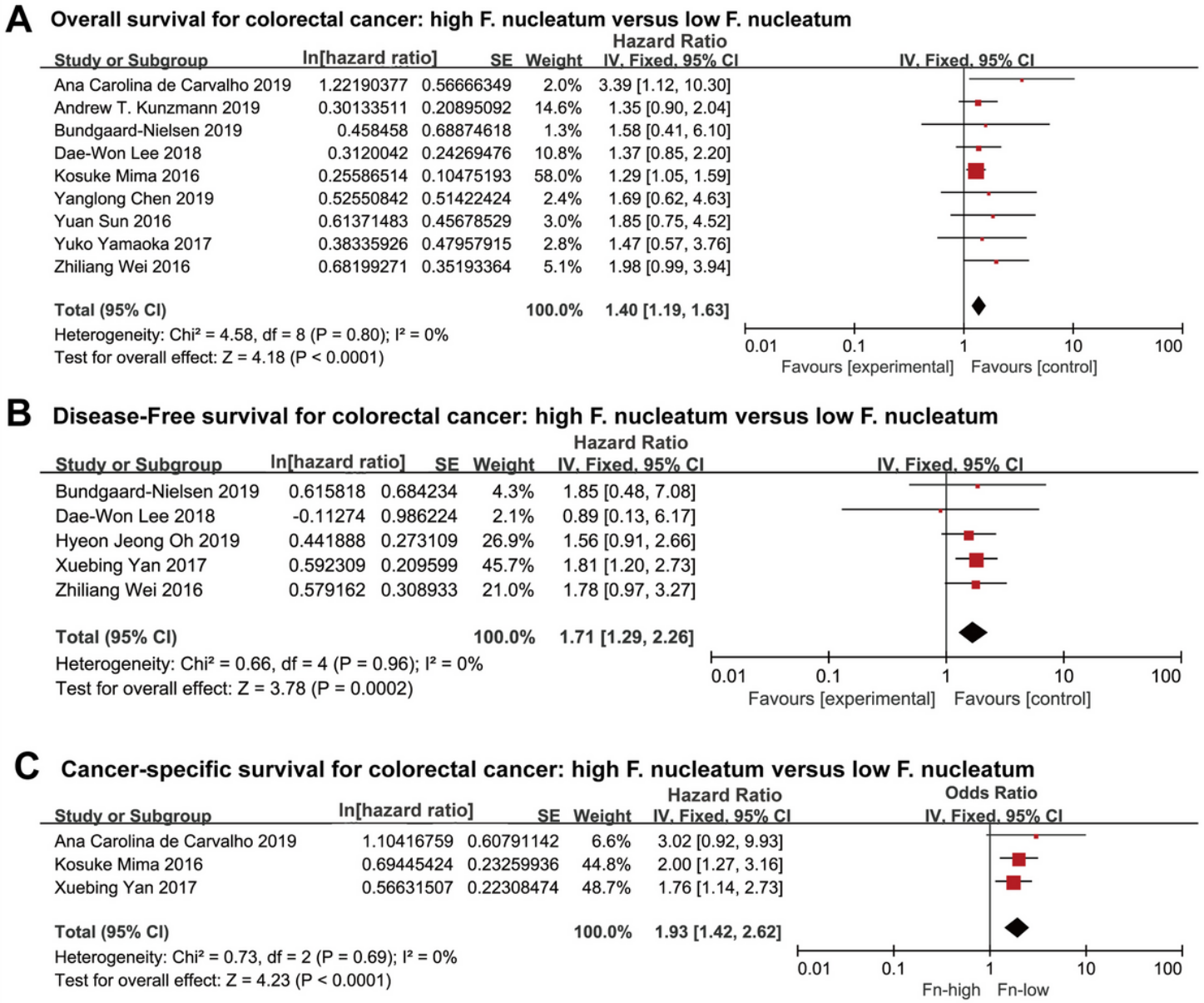

Figure 2

Forest plot for: A. Overall Survival outcomes for colorectal cancer with high level of F.nuleatum versus low level of F.nuleatum; B. Disease-Free Survival outcomes for colorectal cancer with high level of F.nuleatum versus low level of F.nuleatum; C. Cancer-Specific Survival outcomes for colorectal cancer with high level of F.nuleatum versus low level of F.nuleatum

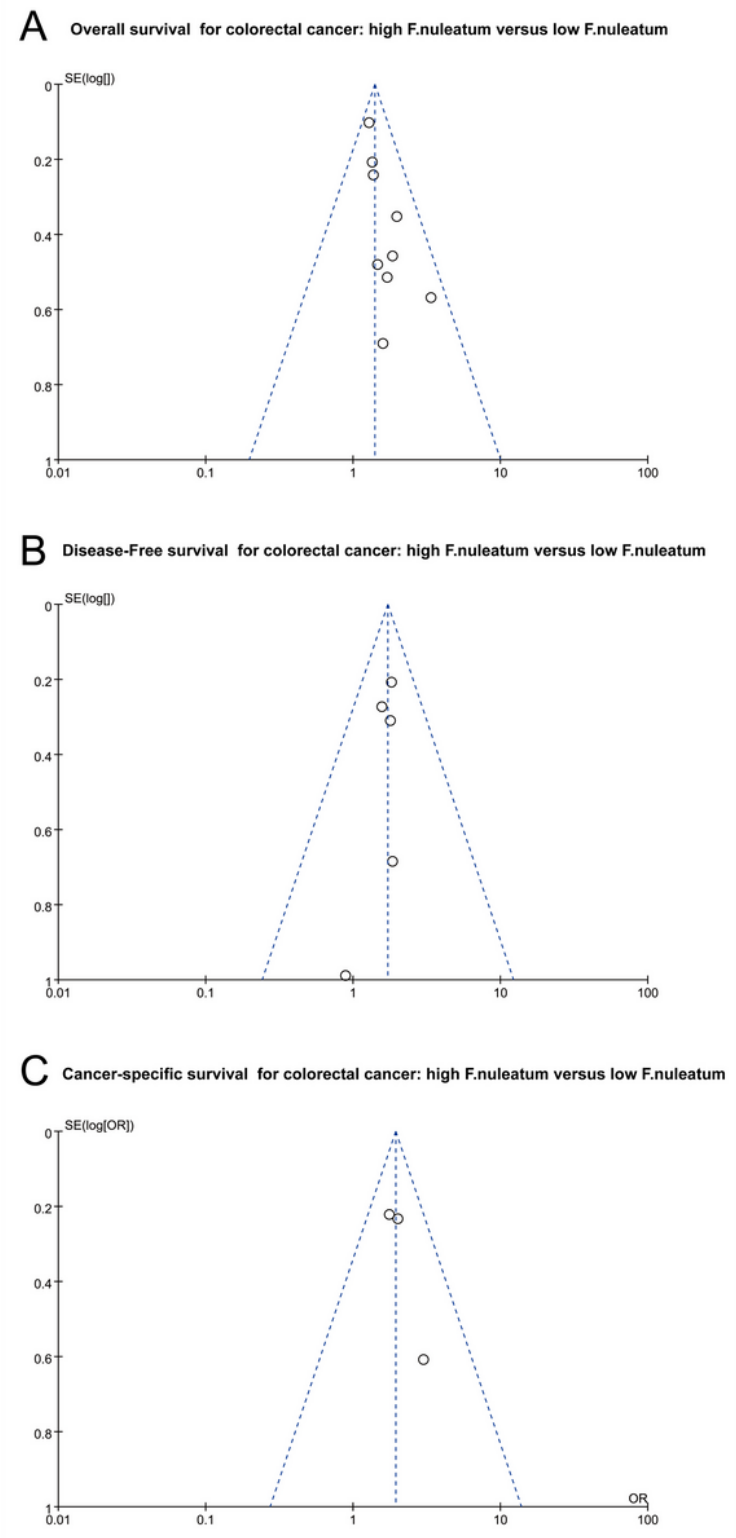

Figure 3

Funnel plots for: A. Overall Survival outcomes for colorectal cancer with high level of F.nuleatum versus low level of F.nuleatum; B. Disease-Free Survival outcomes for colorectal cancer with high level of F.nuleatum versus low level of F.nuleatum; C. Cancer-Specific Survival outcomes for colorectal cancer with high level of F.nuleatum versus low level of F.nuleatum

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- Table4.xlsx
- PRISMA2009ChecklistMSWord.pdf
- Supplemental.pdf