Prognostic Function of Neutrophil-to-Lymphocyte Ratio in Patients with GEP-NEN: A Systematic Review and Meta-Analysis

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Research

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Abstract

Purpose: A high neutrophil-to-lymphocyte ratio (NLR) might be related to unfavorable prognosis. We sought to conduct a systematic review and meta-analysis of published studies exploring the relationship between NLR with the prognosis in patients with gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN).

Methods: The databases PubMed, Embase, and Web of Science were searched using words like 'neutrophil lymphocyte ratio', neuroendocrine tumors', and others through May 2020. We evaluated the significance of NLR on overall survival (OS) and recurrence-free survival (RFS) of patients with GEP-NEN in our study.

Results: We gathered thirteen cohorts with 1598 cases. The pooled analysis revealed that a higher NLR related to worse OS (hazards ratio (HR): 4.59, 95% confidence interval (CI) 3.35-6.29, P < 0.00001) and poor RFS (HR: 4.05, 95% CI: 2.78–5.90, P 0.00001) in patients with GEP-NEN.

Conclusion: A high NLR can be considered a high-risk prognostic factor in GEP-NEN.

1. Introduction

Neuroendocrine neoplasm (NEN) is a group of heterogeneous neoplasms originated from peptidergic neurons and neuroendocrine cells and gastroenteropancreatic neuroendocrine neoplasm accounts for most of this type of tumor [1]. According to the population-based study using nationally representative data from the Surveillance, Epidemiology and End Results (SEER) program, the incidence and prevalence of GEP-NEN are steadily rising, particularly in the small intestine, followed by rectum, appendix, colon, and stomach[2, 3]. Due to the high heterogeneity of this type of neoplasms, effective diagnosis and prognostic evaluation are critical. In recent years, The researchers found that inflammatory response played a decisive role in different stages of tumor development, including initiating, promoting, malignant transformation, invasion, and metastasis[4]. Thus, we sought to conduct a systematic review and meta-analysis of published studies exploring the relationship between NLR with the prognosis in patients with GEP-NEN. We expected that NLR might be an available prognostic factor that could be used in clinical practice.

2. Materials And Methods

2.1 Literature search

We adopted the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements[5] to conduct this meta-analysis. The electronic databases of PubMed, Embase, and Web of Science were searched updated to May 2020. Taking Embase as an example, the following search terms were used: *('neutrophil lymphocyte ratio'/exp OR 'neutrophil to lymphocyte ratio':ti,ab OR 'neutrophil/lymphocyte ratio':ti,ab OR 'nlr (lymphocyte)':ti,ab) AND ('neuroendocrine tumor'/exp OR 'neuroendocrine tumors':ti,ab OR 'neuroendocrine tumour':ti,ab OR 'neuroendocrine tumours':ti,ab)*. All potentially eligible studies irrespective of the primary outcome were considered for review. Other resources were also manually checked for potentially eligible studies. We collected articles only written in the English language. Ethical approval was not necessary since meta-analysis was based on secondary data.

2.2 Inclusion and exclusion criteria

Two investigators (YW and BW) independently evaluated all the candidate articles at different times. Disagreements were resolved by discussion or consultation with another author (YZ). Titles and abstracts were reviewed first to determine whether studies were related to the theme. Then, full articles were judged according to the inclusion and exclusion criteria. If studies satisfied the inclusion criteria, they were used for detailed analysis and data extraction.

The inclusion criteria for eligible studies were as follows: 1. patients with pathologically confirmed GEP-NEN in any stages and classification; 2. the data of OS or PFS was reported in the text or sufficient data were provided to calculate the HR and 95% CI using Tierney method; 3. a definite cut-off value of the NLR was provided; 4. articles published as full-text in English.

The exclusion criteria were as follows: 1. duplicated studies; 2. conference abstracts, reviews, case reports, mete-analysis, letters, animal studies, or laboratory studies; 3. studies lacking necessary data.

2.3 Data extraction and quality assessment

The following information was extracted from each eligible study: name of the first author, year of publication, study area, sample size, study period, gender, mean/median age, study design, tumor stage, intervention methods, the cut-off value of the NLR, HR and 95% CI for OS and/or RFS.

The overall survival time was calculated from the date of treatment initiation to the date of death from any cause of disease. Patients who were still alive were censored at the last follow-up. The recurrence-free survival (RFS) time was calculated as the number of months from the date of surgery to the date of identification of disease recurrence or progression, the date of death or last contact, or the date the endpoint was realized. The NLR was calculated based on pre-treatment laboratory data using the white blood cell (WBC) differential counts with dividing the neutrophil count by the lymphocyte count. OS and RFS outcome expressed as hazard ratio (HR) (and 95% CI) for patients with high NLR versus patients with low NLR;

Quality assessment for the included studies was performed according to the Newcastle–Ottawa scale (NOS). The full score is 9 points, and studies with ≥ 5 points were considered high-quality studies.

2.4 Statistical analysis

The pooled HR with its 95% CI was utilized to quantitatively assess the prognostic significance of the NLR for GEP-NEN patients. Cochrane Q and I^2 tests were used to evaluate the heterogeneity among studies. $P < 0.10$ for the Q test or $I^2 > 50\%$ indicates significant heterogeneity, and the random-effects model is taken. Otherwise, the fixed-effects model is chosen. Subgroup analyses were conducted to examine the prognostic value of the NLR in different populations. If the study reported both univariate and multivariate results, we would uniformly choose the univariate analysis for the final calculation. Sensitivity analyses were performed to confirm the stability of the results. Begg funnel plot test was used to evaluate the publication bias. Review Manager (RevMan 5.3) was used for all statistical analyses. $P \leq 0.05$ was considered statistically significant.

3. Results

3.1 Characteristics of the included studies

The initial search retrieved 204 studies. After the removal of duplicates, 78 studies were excluded. Of the remaining 126 studies, 117 were further eliminated by reading results (titles and abstracts) for the reason of obvious irrelevance. Twenty-one full-text articles were downloaded to assess their eligibility, in which 8 were excluded because non-effective HR data could be collected (n = 2), Conference abstract(n = 17); Data comes from the same sample(n = 2). Ultimately, 13 studies[6–18] published between 2014 and 2020 were included for this meta-analysis, where the sample sizes ranged from 48 to 259, and the total sample size was 1598. (Fig. 1)

The characteristics of the included studies are summarized in Table 1; among them, 12 studies [6–10, 12–18] are retrospective cohort studies, one[11] is a prospective study. In terms of the research area, seven studies[6, 8, 12–16] were performed in China, two[10, 18] in Japan, one[9] in Italy, one[7] in the UK, one[18] in Turkey and one [11] in the USA. Regarding tumor site, seven studies concentrated on pancreatic neuroendocrine neoplasm (P-NEN), three studies enrolled patients with gastric neuroendocrine neoplasm (G-NEN), two studies one study enrolled patients with gastrointestinal and pancreatic neuroendocrine neoplasms (GEP–NEN), one study only included enteric neuroendocrine neoplasms (E-NEN). Twelve studies selected 1.9, 4, 2.6, 3.41, 2.3, 2.31, 1.4, 2.4, 2.8, 2.2, 2.4 and 5 as the cut-off value of the NLR, respectively. According to the NOS score, all the retrospective studies were in high-quality, ranging from 6 to 8 (Table 2).

Table 1
The characteristics of the included studies

No.	Study	Published Year	Area	Sample size	Gender(M/F)	Age(years)	Study period	Study design	Type	Intervention	The cut-off value of NLR	Survi analy
1	Zhou[6]	2020	China	174	82/92	Median 53	2008–2018	Retrospective	P	Surgery	1.9	OS ar RFS
2	Grenader[7]	2020	United Kingdom	201	106/95	Mean 63.68	2006–2013	Retrospective	GEP	lanreotide	4	RFS
3	Pozza[9]	2019	Italy	48	26/22	Median 67	2005–2016	Retrospective	E	Surgery	2.6	OS
4	Zhang[8]	2019	China	156	100/56	Mean 58	2000–2010	Retrospective	G	surgery	2.4	OS ar RFS
5	Harimoto[10]	2019	Japan	55	23/32	Median 61.08	2008–2017	Retrospective	P	Surgery	3.41	RFS
6	Gaitanidis[11]	2018	America	97	47/50	Median 52	UR	prospective	P	34p surgery	2.3	RFS
7	Zhou[12]	2017	China	172	80/92	Mean 52.92	2003–2016	Retrospective	P	Surgery	2.31	OS ar RFS
8	Tong[13]	2017	China	95	39/56	Mean 54.4	2009–2016	Retrospective	P	Surgery	1.4	RFS
9	Luo[14]	2017	China	89	38/51	≥50y, 69 cases and ≤ 50, 96 cases	2006–2015	Retrospective	P	Surgery and others	2.4	OS
10	Fan[15]	2017	China	259	175/84	≥ 60y, 117 cases and<60, 142 cases	2005–2014	Retrospective	GEP	NR	2.8	OS
11	Cao[16]	2017	China	142	103/39	≥70, 114 cases and <70, 33 case	2006–2015	Retrospective	G	Surgery	2.2	OS ar RFS
12	Arima[17]	2017	Japan	58	27/31	Median 58	2001–2015	Retrospective	P	Surgery	2.4	OS ar RFS
13	Yucel[18]	2014	Turkey	52	22/30	≥ 65y, 20 cases and<65y, 32 cases	2006–2012	Retrospective	G	Surgery and others	5	OS

M/F = male-to-female, NOS = Newcastle Ottawa Scale, G = gastric neuroendocrine tumor, E = enteric neuroendocrine tumor, P = pancreatic neuroendocrine tum
Not reported, OS = overall survival, RFS = recurrence-free survival

3.2 Relationship between NLR and overall survival

Nine studies embraced hazard ratio (HR) and 95% CI for OS, and four of them conducted the additional multivariate analysis. As it showed in Fig. 2, in the overall population, A higher NLR was significantly associated to worse OS with a pooled HR of 4.05 (95% CI: 2.86–5.75, P < 0.00001). The heterogeneity analysis among the studies showed an I^2 value of 41% (P = 0.09), which indicated inevitable heterogeneity.

Since the meta-analysis was mainly based on Asian studies, we conducted OS subgroup analysis between Asian and Caucasian (Fig. 3). The subgroup analyses showed that high NLR was both associated with a poor OS for patients in Asian (HR = 4.08, 95% CI 2.71–6.61, P < 0.00001) and Caucasian (HR = 4.54, 95% CI 1.77–11.65, P < 0.05) countries. However, heterogeneity remains high in the pooled data for Asian countries (I^2 value of 55%, P = 0.04)

3.3 Relationship between NLR and RFS

Equally, nine studies embraced hazard ratio (HR) and 95% CI for RFS or DFS, and three of them conducted the additional multivariate analysis. Overall in the population, higher NLR resulted in worse RFS with a pooled HR of 3.16 (95% CI: 2.43–4.10, P<0.00001) with a high level of heterogeneity (I^2 value of 65%, P = 0.003).

The subgroup analyses demonstrated that an elevated NLR indicated a poor RFS in Asian countries (HR = 4.35, 95% CI 2.88–6.57, P < 0.00001) with a low heterogeneity (I^2 value of 36%, P = 0.15) while it was not statistically significant in western data.

3.4 Sensitivity analysis and publication bias

To appraise the effect of each study on the overall outcome, we removed each study individually to conduct a sensitivity analysis. As for OS, when we removed the Fan's research, the pooled HR results changed little, but the heterogeneity declined obviously (I^2 value of 40% with P = 0.4). When excluding other literature one by one, the results were relatively stable. Therefore, Fan's study may be the primary source of high heterogeneity.

As for RFS, we also found an obvious Descending heterogeneity (I^2 value of 34% with P = 0.16) when we removed Grenader's study, which might be the source of heterogeneity.

The shape of the funnel plots showed asymmetry and indicated significant publication bias in OS and RFS. (Fig. 8–9)

4. Discussion

GEP-NEN is the most common type of neuroendocrine tumor. Some researches have found that the prognosis is associated with factors like tumor classification, stage, immunohistochemistry[19, 20]. An accurate and convenient prognostic indicator is needed to assist in clinical decision-making in cancer management. We conducted a meta-analysis by consolidating the published literature to prove the relationship between NLR and the prognosis in patients with GEP-NEN. In the current study, we incorporated 13 studies with 1598 patients to assess the clinical significance of NLR in GEP-NEN. Our research indicated that a high pre-treatment NLR was associated with a poor unfavorable OS and RFS in patients with GEP-NEN.

Several studies have implied that an elevated NLR is associated with the poor survival in several types of cancer, such as esophageal cancer[21], breast cancer[22], colorectal cancer[23], prostate cancer[24] and gynecologic cancers [25]et al. The results of our pooled analysis focus on GEP-NEN agree with results from these abovementioned studies on other cancers.

The relationship between chronic inflammation and cancer has been gradually known in recent years. However, the mechanisms behind the relationship between a high NLR and a worse prognosis in cancer have not been demonstrated. Neutrophils are the most abundant white blood cells in circulation and are the first responders to sites of infection and tissue damage. Tumor-associated neutrophils (TANs) predict poor overall survival in many types of cancer[26]. Persistent inflammation promotes tumor growth, and the chemokines and cytokines, including CXCL8, CXCL5 and CXCL6 generated by tumor cells, and the surrounding microenvironment are involved in neutrophil recruitment[27]. In a broad sense, lymphocytes have anti-tumor activity, so the reduction of lymphocytes is conducive to the maintenance of tumor microenvironment and the growth of tumor cells. These are the possible mechanisms by which high NLR can predict tumor Invasive growth.

We can see that most of the included researches are from China, which may cause selection bias; therefore, a subgroup analysis of the studies based on ethnicity was performed to explore whether race had any effect on the outcome. We considered that a higher NLR is associated with reduced survival time in both Asian and Caucasian. However, the NLR may not be instructive for RFS in Caucasian. In the future, relevant trials are needed to provide further evidence for the prognostic significance of NLR on race. In the sensitive analysis of NLR and OS, we considered that the Fan's study might be the source of high heterogeneity. After the revaluation of its design, sample size, outcome indicators, evaluation criteria, we haven't found apparent defeats. However, it comes from a low-impact journal that can no longer be retrieved by PubMed and is less reliable. As for RFS, after revaluation of Grenader's study that might be the source of heterogeneity, we found that in this study, all patients underwent somatostatin therapy. In contrast, other studies adopted surgical treatments. This indicates that the treatment has a specific effect on the prognosis of GEP-NEN, which may be a confounding factor in NLR prognosis. Overall, the results before sensitive analysis were not robust enough, so after the reassessment, we decided to adopt the pooled HR results after excluding the literature leading to increased heterogeneity.

In our study, there are some limitations. First, 12 of 13 incorporated researches were retrospective studies with small sizes. Second, although most included patients underwent surgical treatment, some patients underwent chemotherapy and somatostatin treatment, which also resulted in a little bit heterogeneity. Third, the study exists a publication bias, as mentioned previously. Fourthly, non-English language literature was not included, and there might be more valuable results that were not included.

5. Conclusion

In conclusion, our meta-analysis demonstrates a high blood-based NLR is related to worse survival in patients with GEP-NEN. NLR may serve as a cost-effective prognostic biomarker to identify high-risk patients who might need further therapy, and there may be other confounding factors, though. More high-quality prospective clinical trials are required to assess the practicability of NLR in GEP-NEN.

Abbreviations

NLR neutrophil-to-lymphocyte ratio; GEP-NEN gastroenteropancreatic neuroendocrine neoplasm; OS overall survival; RFS recurrence-free survival; HR hazards ratio; CI confidence interval; SEER Surveillance, Epidemiology and End Results; PRISMA Preferred Reporting Items for Systematic Review and Meta-Analysis; WBC white blood cell; NOS Newcastle–Ottawa scale; TANs Tumor-associated neutrophils

Declarations

Acknowledgments

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' contributions

YW, ST and LL designed Study, YW and BW searched, and screened literature search, YW and YZ were responsible for the data extraction and analysis, YW wrote the first draft of manuscript, LL had primary responsibility for final content. All authors read and approved the final manuscript.

References

1. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP *et al*: **Gastroenteropancreatic neuroendocrine tumours**. *The Lancet Oncology* 2008, **9**(1):61-72.
2. Patel N, Barbieri A, Gibson J: **Neuroendocrine Tumors of the Gastrointestinal Tract and Pancreas**. *Surgical pathology clinics* 2019, **12**(4):1021-1044.
3. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC: **Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States**. *JAMA oncology* 2017, **3**(10):1335-1342.
4. Grivennikov SI, Greten FR, Karin M: **Immunity, inflammation, and cancer**. *Cell* 2010, **140**(6):883-899.
5. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS medicine* 2009, **6**(7):e1000097.
6. Zhou W, Kuang T, Han X, Chen W, Xu X, Lou W, Wang D: **Prognostic role of lymphocyte-to-monocyte ratio in pancreatic neuroendocrine neoplasms**. *Endocrine connections* 2020, **9**(4):289-298.
7. Grenader T, Pavel ME, Ruszniewski PB, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J *et al*: **Prognostic value of the neutrophil/lymphocyte ratio in enteropancreatic neuroendocrine tumors**. *Anti-cancer drugs* 2020:216-222.
8. Zhang S, Tong YX, Zhang XH, Zhang YJ, Xu XS, Xiao AT, Chao TF, Gong JP: **A novel and validated nomogram to predict overall survival for gastric neuroendocrine neoplasms**. *Journal of Cancer* 2019, **10**(24):5944-5954.
9. Pozza A, Pauletti B, Scarpa M, Ruffolo C, Bassi N, Massani M: **Prognostic role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with midgut neuroendocrine tumors undergoing resective surgery**. *International journal of colorectal disease* 2019.
10. Harimoto N, Hoshino K, Muranushi R, Hagiwara K, Yamanaka T, Ishii N, Tsukagoshi M, Igarashi T, Tanaka H, Watanabe A *et al*: **Prognostic significance of neutrophil-lymphocyte ratio in resectable pancreatic neuroendocrine tumors with special reference to tumor-associated macrophages**. *Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]* 2019, **19**(6):897-902.
11. Gaitanidis A, Patel D, Nilubol N, Tirosh A, Sadowski S, Kebebew E: **Markers of Systemic Inflammatory Response are Prognostic Factors in Patients with Pancreatic Neuroendocrine Tumors (PNETs): A Prospective Analysis**. *Annals of surgical oncology* 2018, **25**(1):122-130.
12. Zhou B, Zhan C, Wu J, Liu J, Zhou J, Zheng S: **Prognostic significance of preoperative neutrophil-to-lymphocyte ratio in surgically resectable pancreatic neuroendocrine tumors**. *Medical Science Monitor* 2017, **23**:5574-5588.
13. Tong Z, Liu L, Zheng Y, Jiang W, Zhao P, Fang W, Wang W: **Predictive value of preoperative peripheral blood neutrophil/lymphocyte ratio for lymph node metastasis in patients of resectable pancreatic neuroendocrine tumors: a nomogram-based study**. *World journal of surgical oncology* 2017, **15**.
14. Luo G, Liu C, Cheng H, Jin K, Guo M, Lu Y, Long J, Xu J, Ni Q, Chen J *et al*: **Neutrophil-lymphocyte ratio predicts survival in pancreatic neuroendocrine tumors**. *Oncology letters* 2017, **13**(4):2454-2458.
15. Fan Y, Ma K, Niu W, Hu Y, Li E, Wu Y: **Prognostic value of pre-treatment prognostic nutritional index is superior to neutrophil to lymphocyte ratio for survival in patients with neuroendocrine tumors**. *International Journal of Clinical and Experimental Pathology* 2017, **10**(2):1719-1728.

16. Cao LL, Lu J, Lin JX, Zheng CH, Li P, Xie JW, Wang JB, Chen QY, Lin M, Tu RH *et al*: **Nomogram based on tumor-associated neutrophil-to-lymphocyte ratio to predict survival of patients with gastric neuroendocrine neoplasms**. *World journal of gastroenterology* 2017, **23**(47):8376-8386.
17. Arima K, Okabe H, Hashimoto D, Chikamoto A, Nitta H, Higashi T, Kaida T, Yamamura K, Kitano Y, Komohara Y *et al*: **Neutrophil-to-lymphocyte ratio predicts metachronous liver metastasis of pancreatic neuroendocrine tumors**. *International journal of clinical oncology* 2017, **22**(4):734-739.
18. Yucel B, Babacan NA, Kacan T, Eren AA, Eren MF, Bahar S, Celasun MG, Seker MM, Hasbek Z: **Survival Analysis and Prognostic Factors for Neuroendocrine Tumors in Turkey**. *Asian Pacific Journal of Cancer Prevention* 2013, **14**(11):6687-6692.
19. Massironi S, Rossi RE, Casazza G, Conte D, Ciafardini C, Galeazzi M, Peracchi M: **Chromogranin A in diagnosing and monitoring patients with gastroenteropancreatic neuroendocrine neoplasms: a large series from a single institution**. *Neuroendocrinology* 2014, **100**(2-3):240-249.
20. Wang YH, Lin Y, Xue L, Wang JH, Chen MH, Chen J: **Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995-2012) in South China**. *BMC endocrine disorders* 2012, **12**:30.
21. Yodying H, Matsuda A, Miyashita M, Matsumoto S, Sakurazawa N, Yamada M, Uchida E: **Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis**. *Annals of surgical oncology* 2016, **23**(2):646-654.
22. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E: **Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis**. *Breast cancer research : BCR* 2017, **19**(1):2.
23. Haram A, Boland MR, Kelly ME, Bolger JC, Waldron RM, Kerin MJ: **The prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer: A systematic review**. *Journal of surgical oncology* 2017, **115**(4):470-479.
24. Gu X, Gao X, Li X, Qi X, Ma M, Qin S, Yu H, Sun S, Zhou D, Wang W: **Prognostic significance of neutrophil-to-lymphocyte ratio in prostate cancer: evidence from 16,266 patients**. *Sci Rep* 2016, **6**:22089.
25. Ethier JL, Desautels DN, Templeton AJ, Oza A, Amir E, Lheureux S: **Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis**. *Gynecologic oncology* 2017, **145**(3):584-594.
26. Shaul ME, Fridlender ZG: **Tumour-associated neutrophils in patients with cancer**. *Nature reviews Clinical oncology* 2019, **16**(10):601-620.
27. Powell DR, Huttenlocher A: **Neutrophils in the Tumor Microenvironment**. *Trends in immunology* 2016, **37**(1):41-52.

Figures

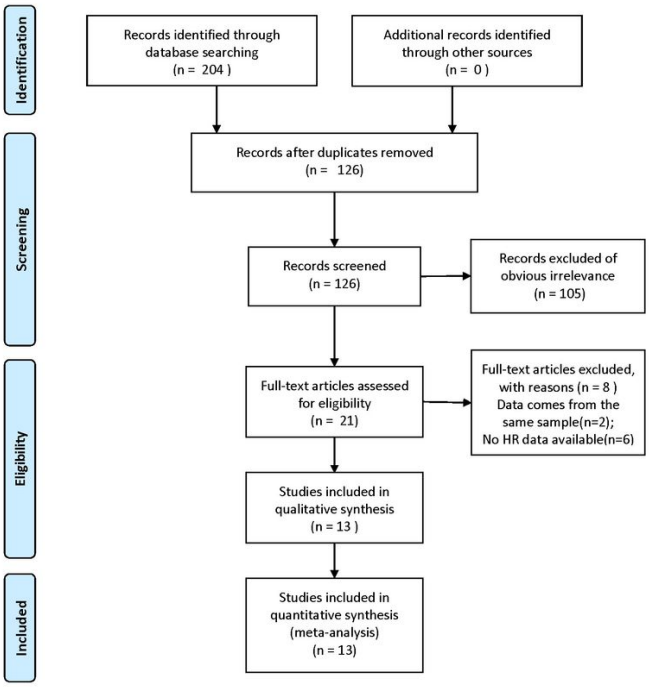

Figure 1

PRISMA flowchart of the study selection process

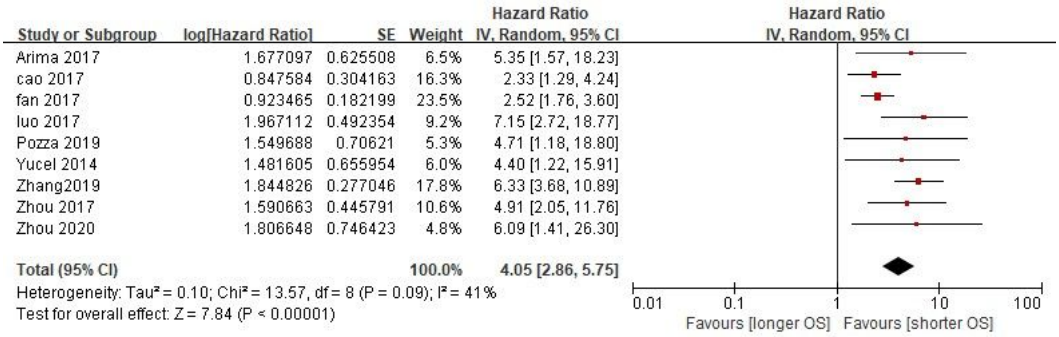

Figure 2

Overall survival analysis in the overall population. Results have been reported considering the hazard ratio of each study, weight of each study and 95% CI of each study. Heterogeneity was estimated through X2, I2 test.

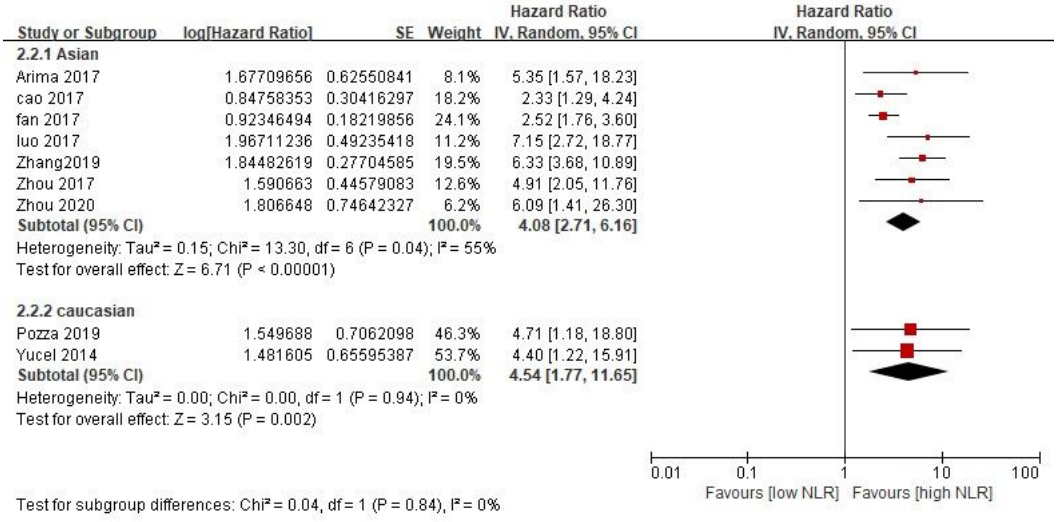

Figure 3

Subgroup analysis of Overall survival analysis in different race population. Results have been reported considering the hazard ratio of each study, the weight of each study, and 95% CI of each study. Heterogeneity was estimated through X2, I2 test.

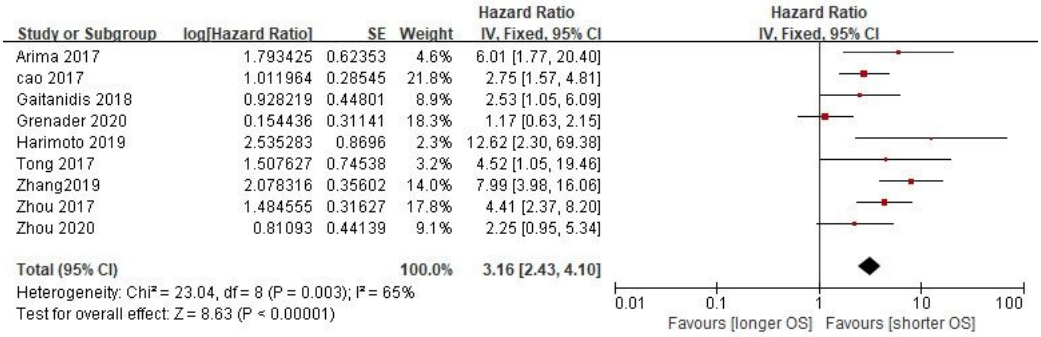

Figure 4

Recurrence-free survival analysis in the overall population. Results have been reported considering the hazard ratio of each study, the weight of each study, and 95% CI of each study. Heterogeneity was estimated through X2, I2 test.

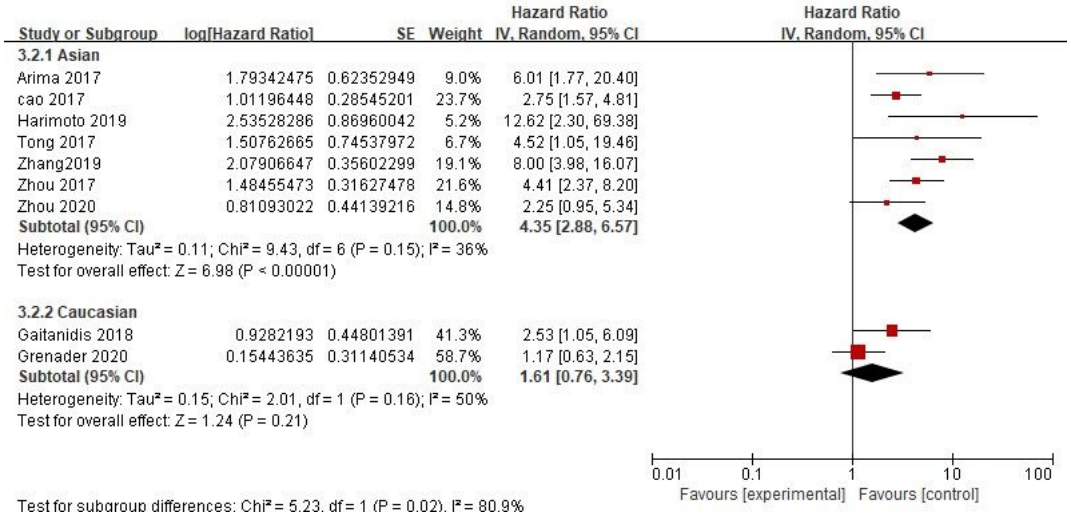

Figure 5

Subgroup analysis of recurrence-free survival in the overall population. Results have been reported considering the hazard ratio of each study, the weight of each study, and 95% CI of each study. Heterogeneity was estimated through X2, I2 test.

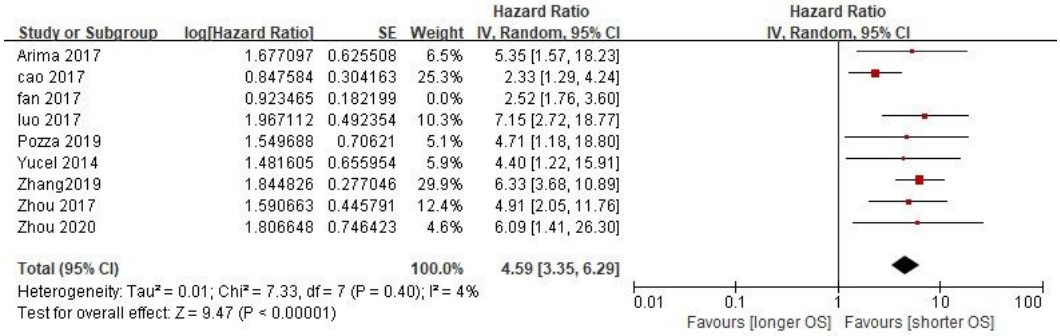

Figure 6

Sensitivity analysis of overall survival. Results have been reported considering the hazard ratio of each study, the weight of each study, and 95% CI of each study. Heterogeneity was estimated through X2, I2 test.

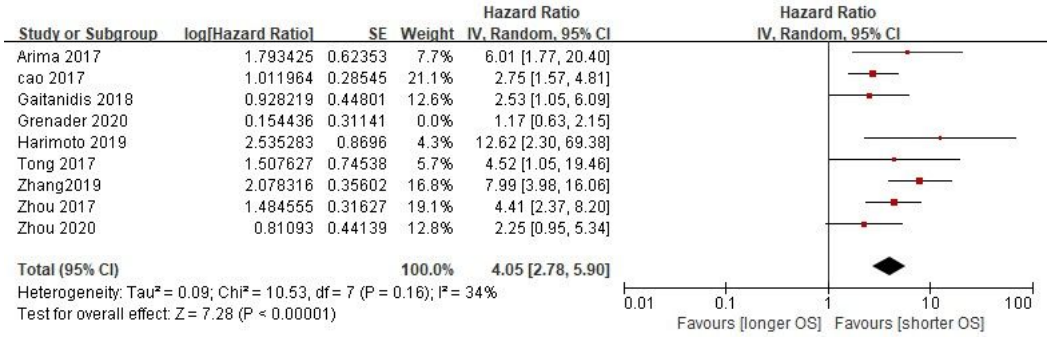

Figure 7

Sensitivity analysis of recurrence-free survival. Results have been reported considering the hazard ratio of each study, the weight of each study, and 95% CI of each study. Heterogeneity was estimated through X2, I2 test.

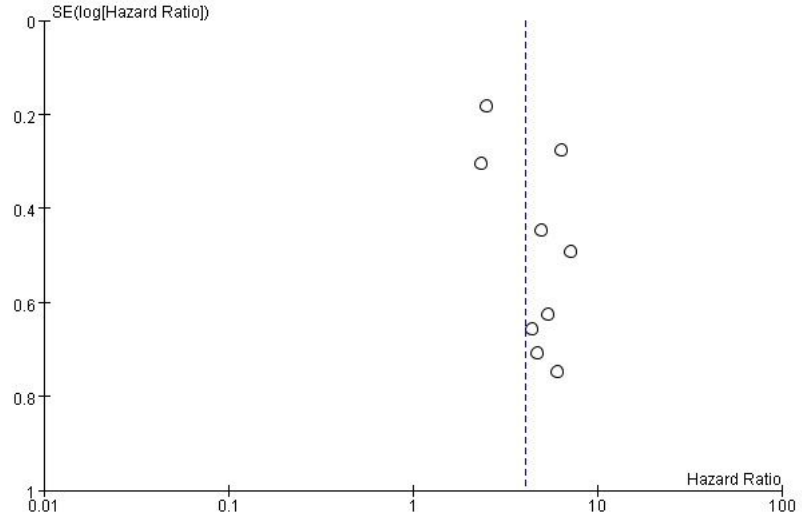

Figure 8

Funnel plot of publication bias test for OS in patients with GEP-NEN

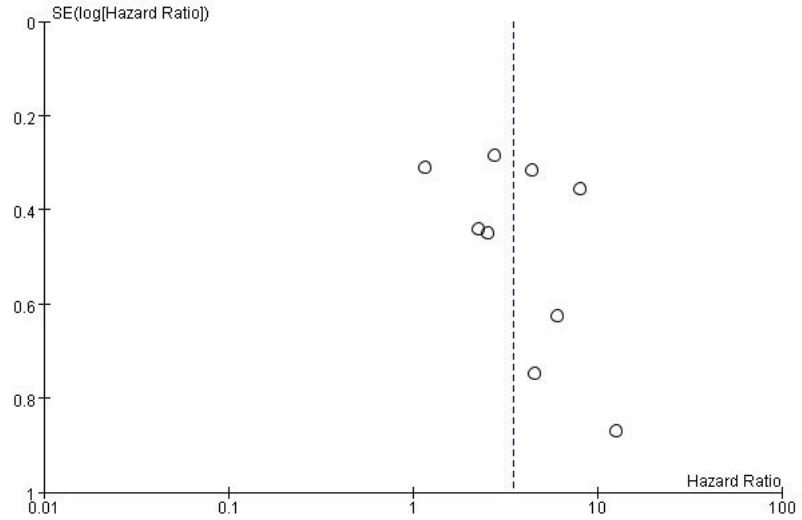

Figure 9

Funnel plot of publication bias test for recurrence-free survival in patients with GEP-NEN