Prognostic Value of Inflammasomes in Head and Neck Carcinoma: A Meta-analysis

Yi-Qun Jia

Stomatology Center, Shenzhen People's Hospital, The Second Clinical Medical College of Jinan University, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong 518020, China

Xiao-Chuan Chen

Department of Stomatology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong 510630, China

Yi-Ming Chen

Department of Stomatology, Huazhong University of Science and Technology Union Shenzhen Hospital, Shenzhen, Guangdong 518020, China

Yu-Yan Zheng

Stomatology Center, Shenzhen People's Hospital, The Second Clinical Medical College of Jinan University, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong 518020, China

Bo Yang (✉ yangb86@mail.sysu.edu.cn)

Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University; Guangdong Provincial Key Laboratory of Stomatology

Research article

Keywords: inflammasome, survival, head and neck carcinoma, meta-analysis

Posted Date: October 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-69346/v1>

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Abstract

Background: Inflammasomes play important roles in responding to insults, triggering inflammation. Nonetheless, their correlation with the prognosis of the head and neck carcinoma (HNC) patients remains controversial.

Methods: In this meta-analysis, we searched 5 inflammasomes in PubMed, Embase and Web of Science databases and included 14 prospective studies with 677 patients. There were two molecules, pyrin domain containing 3 (NLRP3) and Absent In Melanoma 2 (AIM2) satisfied the criteria for further analysis.

Results: Higher expression of both NLRP3 and AIM2 was correlated with longer recurrence-free survival of HNC patients ($P < 0.001$). And higher level of AIM2 expression was associated with better overall survival in HNC patients ($P < 0.001$).

Conclusions: Although publication bias potentially existed, NLRP3 and AIM2 are possible prognostic predictors in HNC patients.

Background

Head and neck carcinoma (HNC) is the sixth most common malignancy worldwide (1), including cancers at oral cavity, pharynx, larynx, paranasal sinus, and so on. Most of head and neck carcinomas are squamous cell carcinoma, although a small amount of them are basaloid squamous cell carcinoma, verrucous carcinoma or other types of cancers (2). According to the statistics, there are over 650,000 new cases of HNC and 35,000 deaths every year (3), most of which are at advanced stage with regional lymph node or even distant metastases (4). In addition, the 5-year survival rate of HNC still remains less than 50% (5–7), which is even worse when HNC is at some specific locations like hypopharynx (8). The conventional treatment strategy for HNC is composed of surgery, chemotherapy and radiotherapy. Recently, immunotherapy and combined therapy are emerging for HNC. However, there are still considerable amounts of patients who don't benefit from the treatments aforementioned. And the specific anatomic locations of HNC and the treatments often result in the damage in speaking, chewing, swallowing, or even breathing, impairing the prognosis of the patients (9). Thus, it is still a must to study further the mechanisms of the carcinogenesis and progression of HNC.

Inflammasomes play an vital role in responding to insults either externally or internally, assembled with nucleotide-binding domain and leucine-rich repeat-containing (NLR) proteins or absent in melanoma 2 (AIM2)-like receptors (ALR), mainly including NLR family CARD domain containing 4 (NLRC4), NLR family pyrin domain containing 1 (NLRP1), NLRP3, AIM2, and so on (10). It activates caspases 1, 11 or 8 (11–13), promoting the production and release of pro-inflammatory cytokines IL-1 β and IL-18 and the cell death (12, 14, 15). What's more, not only are inflammasomes expressed in inflammatory cells, but also capable of initiating inflammatory responses in the cells, like gingival epithelial cells infected by *Porphyromonas gingivalis* in the oral cavity, producing IL-1 β and IL-18 as well (16). And the disturbance of inflammasomes is related with various types of diseases (10, 17), including cancers (13, 18, 19). Among them, inflammasomes are also linked with head and neck cancers. However, although it is reported that some inflammasomes were upregulated in certain kinds of head and neck cancers (20), indicating a poorer prognosis (21), some were unchanged (22) and others even were favorable prognostic markers (23, 24). They may have contradictory functions in promoting antitumor immuno-microenvironment and triggering oncogenic activities (23). These together show us that the roles of inflammasomes in the prognosis of head and neck carcinomas are not illustrated clearly.

In this study, we conducted a meta-analysis of the available literatures on the roles of inflammasomes in predicting the prognosis of head and neck carcinomas in PubMed, Embase and Web of Science. Then we carried out a meta-analysis of the survival rate, including overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) of head and neck carcinoma patients expressing different levels of inflammasomes.

Methods

Literature-search strategy

In this study, literature searching was executed without any restrictions in region, publication type, journal or language on June 10, 2020.. Three databases, PubMed, Embase and the Web of Science were thoroughly searched with the following strategy: (((((((((((((((((((head and neck squamous cell carcinoma[Title/Abstract]) OR head and neck cancer [Title/Abstract]) OR head and neck neoplasm\$[Title/Abstract]) OR HNSCC[Title/Abstract]) OR SCCHN[Title/Abstract]) OR HNC[Title /Abstract]) OR cancers of mouth[Title/Abstract]) OR tongue[Title/Abstract]) OR pharynx* [Title/Abstract]) OR larynx* [Title/Abstract]) OR hypopharynx*[Title/Abstract]) OR nasopharynx* [Title/ Abstract]) OR oropharynx*[Title/Abstract]) OR trachea[Title/Abstract]) OR laryngopharynx* [Title /Abstract]) OR lip [Title /Abstract])OR cervical esophagus[Title/Abstract]) OR cervical tracheal[Title/Abstract])) OR sinonasal[Title/Abstract]) OR head and neck cutaneous squamous cell carcinoma [Title/ Abstract]) OR squamous cell carcinoma of the oral cavity[Title/Abstract])) AND (((((((((((((((((((NLRC4) OR NLR Family CARD Domain Containing 4) OR NOD-Like Receptor C 4) OR CARD12) OR CLAN) OR NLRP1) OR NALP1) OR NLR Family Pyrin Domain Containing 1) OR NLRP3) OR NLR Family Pyrin Domain Containing 3) OR NALP3) OR AIM2) OR Absent In Melanoma 2) OR Caspase 11) OR CASP 11). Yi-Qun Jia and Bo Yang had thoroughly and independently inspected 8 articles met our requirements. Besides, discrepancies were reinspected and resolved by discussion conducted by a senior author (Yu-Yan Zheng).

Inclusion and exclusion criteria

We established several inclusion and exclusion criteria to select candidate studies. There were 4 inclusion criteria as follows: 1) Hazard ratio (HR) and 95% confidence interval (CI) describing correlation between inflammasomes molecules expression level with OS/DFS/RFS in HNC was available or could be estimated; 2) The criteria of diagnosis were reported and at least contained IHC pathological analysis or RNA sequencing; 3) For avoiding duplication, only the most recent article could be selected when multiple studies shared the same population; 4) All the selected articles must be original research.

There were also 6 exclusion criteria as follows: 1) Literature type was confirmed to be meeting abstracts, reviews, or letters; 2) Studies were performed on animal model; 3) Sample size of studies were lower than 30; 4) Articles supplied insufficient data or figure to estimate hazard ratio; 5) Less than three studies were included in analysis of one molecule; 6) Evidence grade of study design was lower than prospective study.

Data extraction and quality assessment

Extraction of data was performed independently by two reviewers (Xiao-Chuan Chen and Yi-Ming Chen), the main datasets from selected articles were as follows: author, year, country or region, ethnicity, location, follow-up period, sample size, gender, cut-off values, detection method, TNM stage, and survival data. The hazard ratio and 95% CI were given in the article, or estimated from the *P* value or Kaplan-Meier survival curve (25, 26).

The quality of selected articles was assessed by two reviewers (Yi-Qun Jia and Bo Yang) by Newcastle-Ottawa Scale (NOS). We gave each study a score of 0–9 by this scale, and all studies with NOS scores higher than 6 were defined as high-quality studies. More importantly, the process of assessing the NOS scores of studies was blinded to the reviewers who extracted the data (Xiao-Chuan Chen and Yi-Ming Chen).

In this part, all disagreements were reinspected by the senior reviewer (Yu-Yan Zheng), then consensus was reached by discussion with all the team members.

Statistical analysis

The procedure and statistical methods of this study were according to recommendations from the Cochrane Collaboration and assessment of article quality was in accordance with Quality of Reporting of Meta-analyses guidelines (27, 28). Hazard ratio was utilized as the significant summary statistic for survival outcomes (OS, DFS, and RFS). In this study, we define a variable as risk factor if the hazard ratio of survival outcomes was higher than 1.

We evaluated the heterogeneity among studies of each group by Cochrane's *Q* statistic and I^2 statistic. If *P* value was lower than 0.10 in Cochrane's *Q* test or an I^2 value was higher than 50%, the consequence suggests substantial heterogeneity in the compared studies. In this situation, random effects model was utilized to evaluate the pooled hazard ratio and 95% CI. Otherwise, there was insufficient heterogeneity which allowed fixed effects model to analysis out data.

We defined the mean of sample size of all studies in current compared group as the standard to classify large and small sample studies. Subgroup were classified according to inflammasome molecule, sample size, ethnicity and tumor location. We used Funnel plots to assess publication bias if the number of studies was higher than 10. Sensitivity analysis was performed by excluding low-quality studies ($NOS \leq 7$) or randomly one study in the group. Statistical analyses in this study were performed with STATA 12.0 statistical software (Stata Corporation, College Station, TX, USA). For the statistical outcome, two-tailed *P* value < 0.05 was defined statistically significant.

Results

Study characteristics

We selected 8 articles from 3 different databases which contained 14 prospective studies. The characteristics and data we extracted from the 14 studies are shown in Table 1. The level of evidence is 3b. All these studies totally included 677 patients meeting the criteria for meta-analysis. Procedure of selecting articles is shown in Fig. 1. Quality of each articles was assessed by NOS (Supplementary Table 1), and each of these articles were published during 2016 to 2020. The majority of selected studies were performed in Asia ($n = 7$), while there was only 1 study performed in Europe ($n = 1$). The majority of the studies researched on the expression level of NLRP3 ($n = 6$), while the remainder researched on that of AIM2 ($n = 3$). Sample sizes of all included studies were generally small, which ranged from 34 to 114. The mean value of all the samples was 84. Consequently, 5 studies were considered relatively large sample size studies ($n > 84$), while the other 3 were small sample size studies ($n \leq 84$). The survival data varied among these studies. There were 6 for OS, 4 for DFS, and 4 for RFS.

Table 1
Characteristics of included studies.

Author year	Target	Country/Region	Ethnicity	Tumor location	Sample size	Gender M/F	Cut-off value	Detection method	TMN stage	Outcome	HR estimation
Wu, et al 2016(29)	NLRP3	Taiwan	Asian	OSCC	113	97/14	Score > 120	IHC	I-V	OS DSS DFS	reported
Chung, et al 2020(20)	NLRP3	Taiwan	Asian	NPC	49	NA	Score $\geq$ 130	IHC	I-V	RFS	reported
Riva, et al 2019(22)	AIM2	Italy	Caucasian	HNSCC	34	24/10	Upregulated/ downregulated	RT-qPCR	I-V	OS DFS	reported
Chen, et al 2017(23)	AIM2 NLRP3	Taiwan	Asian	NPC	114	NA	Score > 140 (AIM2), score > 160 (NLRP3)	IHC	NA	RFS	reported
Feng, et al 2017(30)	NLRP3	China	Asian	OSCC	103	63/40	Grade > 2	IHC	I-V	OS DFS	reported
Xue, et al 2019(21)	NLRP3	China	Asian	LSCC	104	103/1	Grade > 1	IHC	I-V	OS DFS	reported
Li, et al 2016(24)	AIM2	China	Asian	HSCC	111	93/18	Grade > 1	IHC	I-V	OS	reported
Xu, et al 2019(31)	NLRP3	China	Asian	LSCC	49	NA	Grade > 2	IHC	I-V	OS RFS	reported
M/F: male/ female; NA: not available; OSCC: oral squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; NPC: nasopharyngeal carcinoma; LSCC: laryngeal squamous cell carcinoma; cut-off value: the value that can be diagnosed as a positive/high expression of inflammasome molecules; IHC: Immunohistochemistry; RT-qPCR: quantitative reverse transcription polymerase chain reaction; OS: overall survival; DFS: disease-free survival; DSS: disease-specific survival; P: prospective; NOS: Newcastle–Ottawa Quality Assessment Scale.											

Methodological quality of the included studies

We evaluated the quality of all the selected 14 studies in 8 articles. Majority of these studies given the length of follow-up period, which were more than five years. Therefore, the quality of the studies was generally high. However, few of studies had represented adequate detailed characteristics of the population. Strategy to deal with loss of follow-up and intention-to-treat of subjects were not thoroughly described in most of the studies.

Inflammasome molecule expression and prognosis of HNC patients

Six studies with totally 514 subjects reported the correlation between OS and two inflammasome molecules in HNC. Protein level of both molecules was detected except for one study evaluated mRNA levels of *AIM2*. High level or low level of expression was defined according to cut-off criteria as presented in Table 1. We pooled all data in the same type of survival data, the relationship between overexpression of these molecules and OS was not significant (HR = 1.29; 95% CI: 0.49–3.39, $P = 0.612$; Table 2). The overall heterogeneity was obvious ($I^2 = 74.6\%$, $P_h < 0.001$; Fig. 2). Moreover, similar result was obtained for that of DFS (Fig. 3).

Table 2
Results of the meta-analysis on the prognostic effects of inflammasome molecules in HNC patients

	Variable	Study no.	Sample size	HR (95% CI)	Pvalue	Heterogeneity	
						I ²	Pvalue
OS	Overall	6	514	1.285 (0.487-3.395)	0.612	74.6%	<0.001
	Inflammasome molecules						
	NLRP3	4	369	1.880(0.696-5.079)	0.213	66.0%	0.032
	AIM2	2	145	0.353(0.188-0.663)	0.001	0.0%	0.996
	Ethnicity						
	Asian	5	480	1.295(0.478-3.507)	0.611	79.7%	<0.001
	Caucasian	1	34	0.121 (0.000-e ¹⁹⁷)	0.993	-	-
	Tumor location						
	OSCC	2	216	1.419 (0.269-7.494)	0.680	72.3%	0.057
	HNSCC	1	34	0.121 (0.000-e ¹⁹⁷)	0.993	-	-
	LSCC	2	153	2.683 (0.551-13.052)	0.221	70.1%	0.067
	HSCC	1	111	0.353 (0.188-0.663)	0.001	-	-
	Sample size						
	Large	4	431	1.349 (0.379-4.800)	0.644	83.8%	<0.001
	Small	2	83	1.300(0.486-3.479)	0.601	0.0%	0.992
DFS	Overall	4	354	1.880 (0.473-7.474)	0.370	68.5%	0.023
RFS	Overall	4	326	0.216 (0.116-0.402)	<0.001	0.0%	0.545

Four studies with 326 patients reported the relationship between RFS and at least one of the two inflammasome molecules in HNC. All the expression of both molecules was detected mainly at the protein level by IHC. Overexpression was also defined as presented in Table 1. When the data for both two molecules were pooled, there was significant relationship between the overexpression of these molecules and RFS (HR = 0.22; 95% CI: 0.12–0.40, $P < 0.001$; Fig. 4), and there was no overall heterogeneity ($I^2 < 0.1\%$, $P_h = 0.545$; Fig. 4)

Subgroup analyses

Subgroup analyses of OS data stratified according to the inflammasome molecule, ethnicity, tumor location and sample size were performed to detect potential sources of heterogeneity (Table 2). In the stratification based on the inflammasome molecule, longer OS was consistently found in patients with higher levels of AIM2, correlating with a longer prognosis (HR = 0.35, 95% CI: 0.19–0.66, $P < 0.001$, Fig. 2, Table 2). Besides, the studies of AIM2 subgroup were not sources of heterogeneity ($I^2 < 0.1\%$, $P_h < 0.001$; Fig. 2, Table 2). However, no obvious trend in OS data was found according to tumor location and sample size (Table 2).

Sensitivity analysis and publication bias

A sensitivity analysis of the association between the expression of inflammasome molecules and the OS of HNC patients was performed for high-quality studies (NOS score ≥ 7 , Fig. 5). The overall HRs and 95% CIs followed the same trends as those in the previous analysis. In addition, we excluded each of the four studies to evaluate the sensitivity of the association between the expression of inflammasome molecules and the RFS of HNC patients. The results remained to suggest higher expression of inflammasome molecules were correlated with longer RFS of HNC patients, and there were no significant heterogeneity among these studies (Supplementary Fig. 1–4).

Funnel plots of all the 14 studies combined with OS, DFS, and RFS were created (Fig. 6). For all these plots, the studies were distributed uniformly around the axis, manifesting no obvious publication bias (Egger's test, $P = 0.467$). However, the number of each subgroup of OS, DFS, or RFS was not eligible to Egger's test (total number < 10), suggesting that publication bias potentially existed in the conclusion.

Discussion

Inflammasomes were initiated by insults both from outside and inside the human body and expressed in diverse types of cells, facilitating maturation of inflammatory cytokine production. As inflammatory storms may promote the carcinogenesis (32, 33), they may have relationships with cancer formation. In recent years, inflammasomes have been reported with higher or lower levels in HNCs, especially NLRP3 (20, 21, 23, 29–31) and AIM2 (22–24). However, no agreement has been reached on the relationships between inflammasomes and the prognosis of HNC.

This meta-analysis on the prognostic value of inflammasome molecules included 14 studies with a total of 677 patients. The expression of inflammasome molecules was found to be a controversial prognostic factor for the OS, DFS, and RFS of HNC patients (34–38). Although the current view is that inflammasome molecules may be important predictors of a poor prognosis in HNC (36), we found that higher expression of inflammasome molecules was associated with longer RFS of HNC patients. What's more, higher level of AIM2 correlated with longer OS of HNC patients. However, the number of each subgroup of studies was less than 10, which did not meet the requirement for Egger's test to verify the public bias. Thus, our results require careful attention.

NLRP3 and AIM2, among inflammasomes, were reported in the included articles and studies, predicting longer RFS. The microorganisms in head and neck cancers were different from those in normal tissues (39, 40), whose products could prompt the cells to generate hydrogen peroxide and thus stimulate NLRP3 activation. They also induced the DNA damage, activating AIM2 inflammasome. Similar situations were also reported, for instance, HCV in liver cancer (41), *Helicobacter* in gastric cancer (42) or EBV in NPC (23) could also promote the expression of inflammasomes. The elevated inflammasomes could facilitate the maturation of IL-1 β and inflammation. And IL-1 β could recruit neutrophil infiltration (23). This might be one of the mechanisms accounting for higher levels of inflammasomes indicating better prognosis of head and neck cancers.

And AIM2 was found correlated with longer OS in HNC patients in our meta-analysis. During cellular pathogenic assault, AIM2 recognizes double-stranded DNA (dsDNA) released as a cytosolic innate immune receptor (43). Expression level of AIM2 in early gastric cancer tissues is lower than that in progressive gastric cancer tissues, which suggests AIM2 is one prognostic markers and promising therapeutic targets in patients (23, 37). However, AIM2 is highly expressed in non-small cell lung cancer (NSCLC) cells and that high AIM2 expression is associated with poor prognosis in patients with NSCLC (44). Our data revealed high expression of AIM2 in HNC was associated with better overall survival, this consequence needs to be reconfirmed by researches with larger samples.

Several limitations exist in this meta-analysis. Firstly, the number of each subgroup of studies is less than 10, which means it cannot meet the requirements of Egger's test to analysis the publication bias. Secondly, all the of studies did not have adequate random sequences or comparable cohorts, increasing the risk of bias. Lastly, the majority of study populations were Asian ethnicity, which may have caused a population selection bias.

Conclusions

In summary, our meta-analysis indicated that inflammasomes, including NLRP3 and AIM2 correlated with better prognosis in HNC patients: higher level of both NLRP3 and AIM2 were associated with a longer RFS and higher level of AIM2 predicted a longer OS. Inflammasomes have potential prognostic values and applicability as therapeutic targets for HNC.

List Of Abbreviations

HNC: Head and neck cancer; NLRP3: NOD-like receptor family, pyrin domain containing 3; AIM2: Absent In Melanoma 2; NLR: Nucleotide-binding domain and leucine-rich repeat-containing; ALR: AIM2-like receptors; NLRC4: NLR family CARD domain containing 4; NLRP1: NLR family pyrin domain containing 1; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence-free survival; HR: Hazard ratio; CI: Confidence interval; NOS: Newcastle–Ottawa Scale; dsDNA: double-stranded DNA; NSCLC: Non-small cell lung cancer.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the funds received by B.Y. from Fundamental Research Funds for the Central Universities (20ykpy80) and by C.X.C. from Medical Research Foundation of Guangdong Province (A2020400).

Authors' contributions

X.C.C. and Y.M.C. extracted the information independently from the included studies. Y.Q.J. and B.Y. independently assessed the quality of the included studies, and they were major contributors in writing the manuscript. Consensus was reached by discussion with Y.Y.Z. when there were inconsistent results. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

Figure 1

Flow diagram of studies identified, included and excluded.

Figure 2

Overall forest plot of stratified analysis based on the type of molecule for the association of inflammasome molecules with OS.

Figure 3

Overall forest plot of stratified analysis for the association of inflammasome molecules with DFS.

Figure 4

Overall forest plot of stratified analysis for the association of inflammasome molecules with RFS.

Figure 5

Overall forest plot of stratified analysis based on the high-quality studies for the association of inflammasome molecules with RFS.

Figure 6

Begg's funnel plots of publication bias on the relationships between inflammasome molecules and OS in all studies.

Supplementary Files

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