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Impact of prior extrapulmonary cancer on survival after lung cancer: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This review aimed to examine the impact of previous extrapulmonary malignancies on the overall survival (OS) of lung cancer patients.

MATERIALS AND METHODS: The online databases of PubMed, Embase, Scopus, and Web of Science were explored for studies published up to 22nd December 2022 and comparing outcomes of first lung cancer vs. second primary lung cancer with a history of previous extrapulmonary malignancy. Studies were to report adjusted data on OS. Meta-analysis was performed in a random-effects model.

RESULTS: Nine retrospective studies were eligible. A total of 267,892 lung cancer patients with prior extrapulmonary malignancy and 1,351,245 primary lung cancer patients were analyzed in the studies. Meta-analysis of all studies showed that prior extrapulmonary malignancy results in poor OS in lung cancer patients as compared to those with no history of such cancer (HR: 1.27 95% CI: 1.07, 1.50 I^2=83%). The results did not change on sensitivity analysis. No publication bias was noted.

CONCLUSIONS: The result of this meta-analysis indicates that a history of prior extrapulmonary malignancy results in poor OS in patients with lung cancer. Caution is needed in the interpretation of the results owing to high interstudy heterogeneity. Further research is needed to assess how factors like the type of extrapulmonary malignancy, time interval of diagnosis, cancer stage, and treatment modality impact this relationship.

Key Words:
Lung malignancy, Second cancer, Survival, Mortality.

Introduction

Lung cancer is among the most prevalent malignancies and leading cause of cancer-related death worldwide[1]. Each year roughly two million individuals are diagnosed with lung cancer contributing to nearly 12% of all cancers seen globally[2]. Broadly, non-small cell and small cell lung cancer represent the major histological types with the former accounting for nearly 2/3rd of the cases[3]. Since most of the individuals with lung cancer present in advanced stage with local or distal metastasis, such tumors are frequently non-operable resulting in poor overall survival (OS)[4]. However, with advancements in surgical techniques and pharmaceutical research leading to the use of robotic surgeries, immunotherapy, and molecular targeted therapies, the management of lung cancer has vastly improved in the last decade[5]. Nevertheless, OS with lung cancer is still poor with 5-year figures reaching 19% only[2]. It is well known that numerous factors can influence cancer survival[6,7]. Importance of patient survival is not only for treating clinicians but also nursing personnel involved in patient care. Nursing personnel are closely involved during chemotherapy, radiotherapy, and even surgical intervention of lung cancer patients and hence they should be well-versed with factors influencing patient survival. In this context, it is necessary that factors resulting in poor OS are well recognized in order to aid in accurate prognostication of lung cancer[6,7].

In recent years, lung cancer has emerged as a common second primary malignancy in adults[8]. As the survival with other extrapulmonary cancers is improving, therapy for treatment of the primary malignancy can lead to development of secondary cancers. According to one study[9], patients with breast cancer receiving radiation have a 22% increased risk of lung cancer as a second primary malignancy. Indeed, management strategies in lung cancer patients with prior extrapulmonary malignancies may change based on the ability of the patient to tolerate a second surgery or a second radiotherapy/chemotherapy protocol. Also, lung cancer patients with prior malignancies are frequently excluded from clinical trials owing to an assumed higher risk of poor survival[9].

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Such prejudiced approach can influence clinical decisions to dispense or withhold potentially curative therapy. Over the past decade, several studies[10-12] have researched on the influence of prior cancers on outcomes of lung cancer but with mixed results. To date, no systematic review has been attempted to provide clarity on the topic. Hence, the current study was undertaken to analyze the impact of prior extra-pulmonary malignancies on OS of lung cancer *via* a meta-analytic approach.

Materials and Methods

Protocol Registration

The protocol of the study was preregistered on the PROSPERO database managed by the National Institute for Health Research, University of York, Center for Reviews and Dissemination, and was given the registration number (CRD42022385238). The manuscript was written according to the protocols of the PRISMA statement[13].

PECOS Inclusion Criteria

The following PECOS framework was generated for searching studies for inclusion:

- Population: Lung cancer patients.
- Exposure: Prior history of extrapulmonary malignancy.
- Comparison: No prior history of extrapulmonary malignancy.
- Outcomes: OS.
- Study type: All types.

We did not use any restrictions based on the type of prior extrapulmonary malignancy or the treatment protocols used for either cancer.

Exclusion Criteria

The following studies were excluded: 1. Studies not reporting data on OS as adjusted ratios 2. Studies on simultaneous presentations of lung cancer and extrapulmonary cancer 3. Studies not reporting separate data for prior extrapulmonary malignancies 4. Studies with overlapping or duplicate data (in such cases the study with maximal sample size was included).

Search Methods

A detailed search was carried out by two reviewers separately on the online databases of PubMed, Embase, Scopus, and Web of Science. Gray literature was explored using the database of Google Scholar. All articles published between the inception of the databases to 22nd December 2022 were searched using the search terms: "lung cancer", "prior cancer", "previous cancer", "previous malignancy", "metachronous cancer", AND "second lung cancer". There was no restriction on the language of publication. All search results were examined first by their titles and abstracts to identify studies relevant to the review. The selected full texts were read by the two reviewers independently and any disagreements were resolved by discussion. A manual search of the referenced studies among the included studies was also conducted.

Data Extraction and Risk of Bias

Two reviewers were involved in data extraction which included: the first author, publication year, study type, databased used, use of propensity score matching, sample size, age and gender, lung cancer treatment, the time between prior cancer and second lung cancer, type of prior lung cancer, follow-up, and outcome ratio. In case of missing data, the corresponding author was contacted once by email. Only adjusted data on OS were extracted and pooled in the review.

As all studies were observational, the quality of studies was examined by the Newcastle-Ottawa scale (NOS)[14]. It was done by two reviewers independently and any disagreements were solved by a discussion with the third reviewer. The NOS awards stars for the selection of study population, comparability, and outcomes. These are given a maximum of four, two, and three points respectively.

Statistical Analysis

The software "Review Manager" [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark; 2014] was used for the meta-analysis. Hazard ratios with 95% confidence intervals (CI) were combined by the generic inverse variance function of the Review Manager to generate the pooled result. The random-effects model was chosen. Heterogeneity was assessed using the I^2 statistic. I^2 values of <50% represented low and >50% represented high heterogeneity. Publication bias was checked by using funnel plots. We also conducted a sensitivity analysis wherein individual studies were excluded one at a time to check the significance of the results. Subgroup analyses were conducted based on study location (Asian *vs.* non-Asian), type of prior cancer, and treatment of lung cancer. A p-value of <0.05 was statistically significant.

Results

The number of studies at each stage of the search protocol is shown in Figure 1. 8,769 studies were found after the entire search. 4,913 were excluded during deduplication. 3,856 studies were screened and 28 were selected for full-text review. Of these 19 were excluded and finally, nine were included in this review[8,10-12,15-19].

Details extracted from the studies are shown in Table I. The studies were retrospective and conducted in the USA, Spain, France, Japan, China, and Taiwan. Only one study[16] used a matching of study groups for baseline variables. A total of 267,892 lung cancer patients with prior extrapulmonary malignancy and 1,351,245 primary lung cancer patients were analyzed in the studies. Three studies[8,12,17] included lung cancer patients undergoing all kinds of treatments while the remaining included surgical cases only. The type of prior malignancy was mixed in all studies except for two (One[16] on head and neck cancer and the other[10] on gastric cancer). The NOS score of the studies was 7 or 8.

Meta-analysis of all studies[8,10-12,15-19] showed that prior extrapulmonary malignancy results in poor OS in lung cancer patients as compared to those with no history of such cancer (HR: 1.27 95% CI: 1.07, 1.50 I^2=83%) (Figure 2). The results did not change on sensitivity analysis. No publication bias was noted (Figure 3).

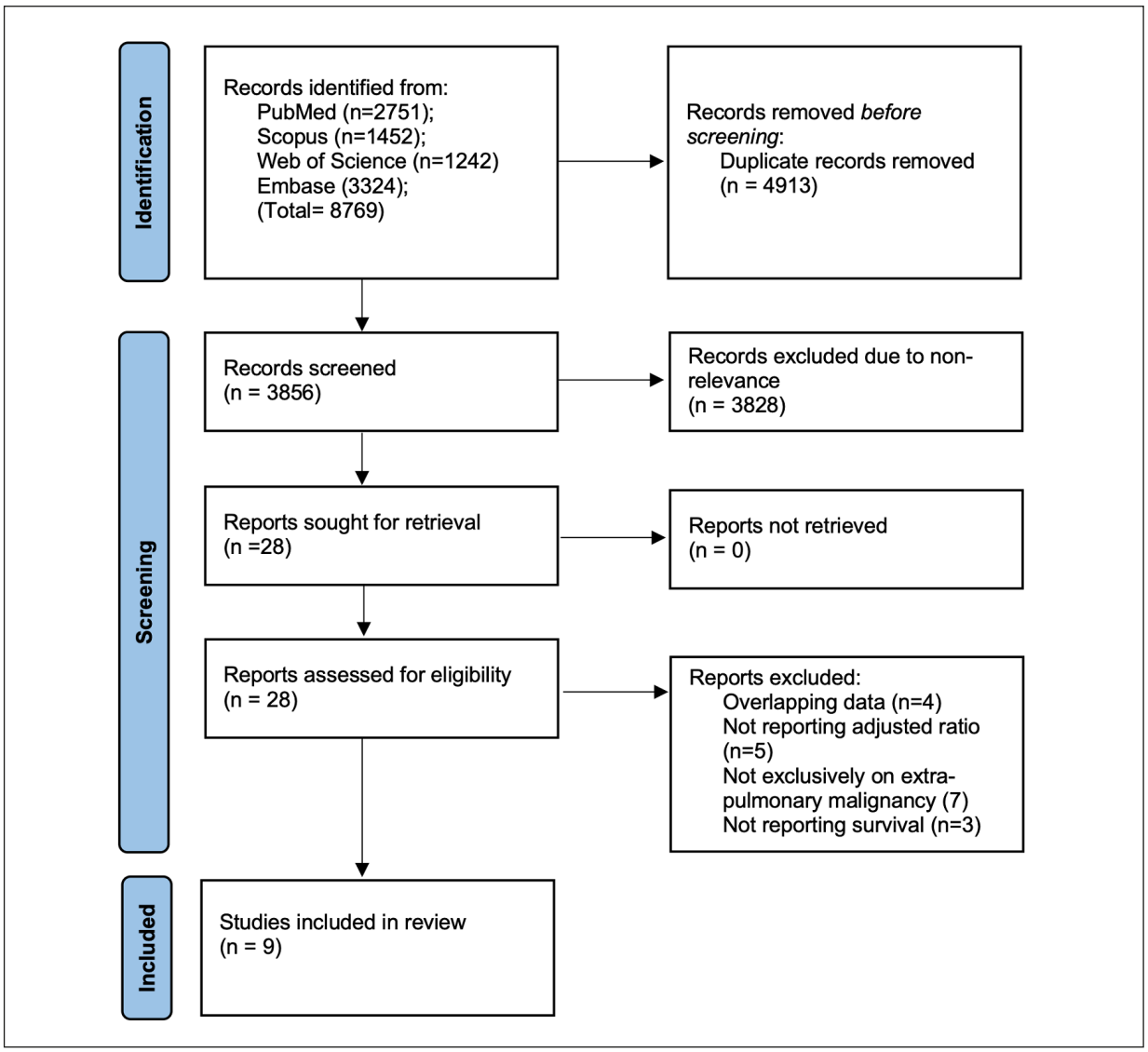


Figure 1. Study flowchart.

Table I. Details of included studies.

Study	Database	Location	Matching of groups	Groups	Sample size	Age (years) (%)	Male gender	LC treatment and second LC	Time between prior cancer	Type of prior cancer	Follow up	NOS score
Takatsu 2022[16]	Okayama University Thoracic Surgery Study Group	Japan	Yes	Primary LC Second LC	200 100	70.9± 7.7 70.8± 8.5	91.5 91	Surgery	Median 41 months	Head and neck	Median 50.1 months	8
Li 2022[19]	Fudan University	China	No	Primary LC Second LC	15963 1469	NR	NR	Surgery	NR	Mixed	NR	7
Lee 2021[18]	National Taiwan University Hospital	Taiwan	No	Primary LC Second LC	2208 200	60.3± 11.2 62± 11.3	32.7 29	Surgery	Mean 5.4 years	Mixed	Mean 39.1 months	8
Nakao 2019[15]	University of Tokyo	Japan	No	Primary LC Second LC	682 196	69.2± 10 66.5± 10	61.5 69.7	Surgery	NR	Mixed	Median 7.5 years	8
Monsalve 2019[17]	National Cancer Database	USA	No	Primary LC Second LC	641811 179512	NR	54.2 54	Mixed	NR	Mixed	Median 38.4 months	8
Deng 2019[8]	SEER (1988-2014)	USA	No	Primary LC Second LC	679541 85758	NR	54.1 59.7	Mixed	Median 4.8 years	Mixed	Median 0.6 years	7
Tsubokawa 2015[10]	Multicentric	Japan	No	Primary LC Second LC	4551 100	66.2± 9.7 70.9± 7.6	61 85	Surgery	Median 3.2 years	Gastric	Median 62.3 months	8
Pagesa 2013[11]	Georges Pompidou European Hospital and Cedar Surgery Centre	France	No	Primary LC Second LC	4603 389	61± 10.2 65.7± 9.4	81.8 66	Surgery	Mean 87 months	Mixed	Mean 72.8 months	8
Aguilo 2008[12]	Tumor Registry of Hospital del Mar	Spain	No	Primary LC Second LC	1686 168	NR	NR	Mixed	NR	Mixed	NR	7

LC, lung cancer; NOS, Newcastle Ottawa scale; NR, not reported

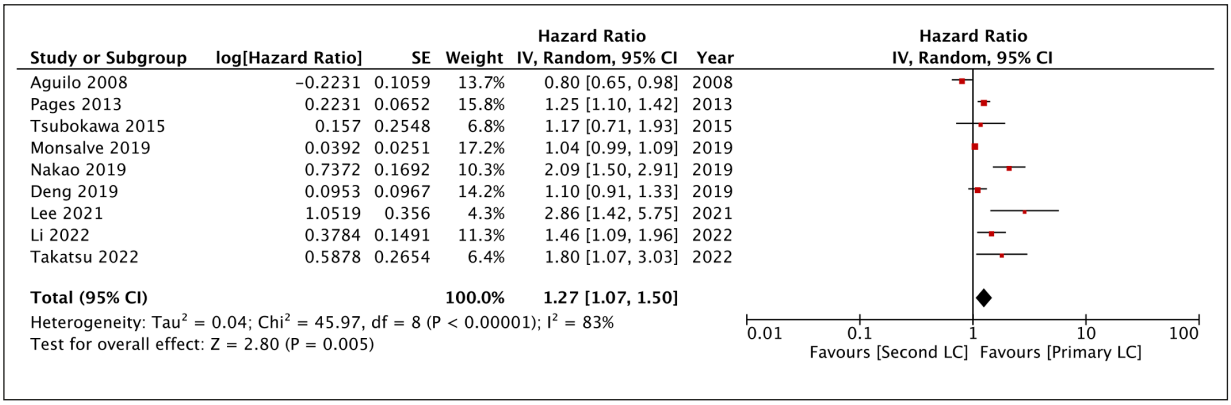
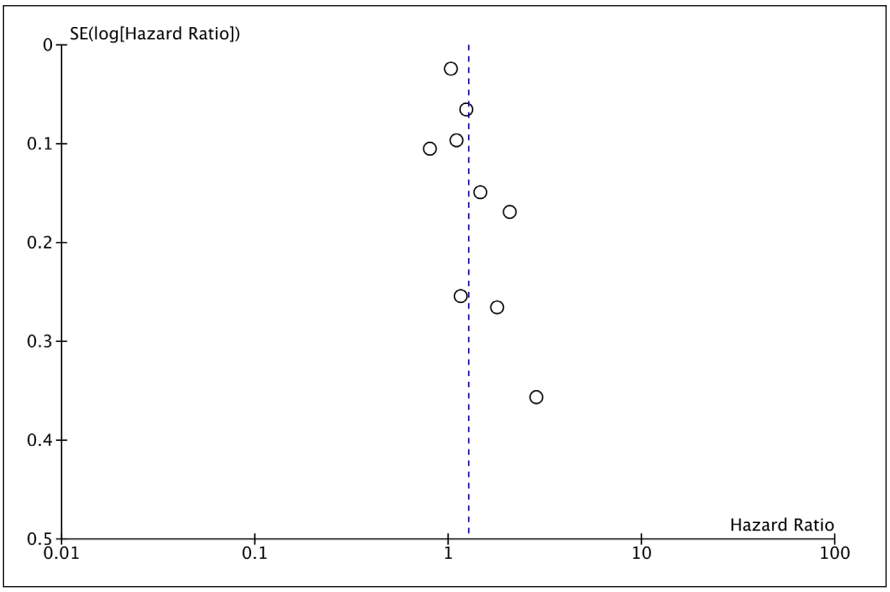


Figure 2. Meta-analysis of OS for lung cancer patients with and without a history of prior malignancy.

Figure 3. Funnel plot to assess publication bias.



The results of subgroup analyses are shown in Table II. When divided based on location, it was noted that the results were significant only for studies on the Asian population but not on the non-Asian population. Also, the results were significant only for studies including lung cancer patients treated with surgery but not for mixed populations.

Discussion

To summarize, this is the first meta-analysis assessing the impact of prior extrapulmonary malignancy on the outcome of lung cancer. We included nine observational studies with a total sample size of approximately 1.6 million patients. The result showed that prior cancer does lead to poor survival in lung cancer patients but with high inter-study heterogeneity.

Management of cancer patients has seen tremendous progress in the past few decades with rapid development in diagnostic and therapeutic modalities[20]. Immunotherapy and targeted molecular therapies, robotic surgeries, focused radiotherapy, and high-quality nursing care have improved outcomes for patients who now survive long and may develop a second primary malignancy. Furthermore, improvement in cancer detection with the aid of advanced imaging and new biomarkers has increased the discovery of multiple primary cancers[21,22]. Multiple primary cancers can be described as the presentation of two or more synchronous or metachronous can-

Table II. Subgroup analysis.

Variable	Groups	Studies	Hazard ratio
Location	Asian	5	1.72 95% CI 1.33, 2.2 I2=42%
	Non-Asian	4	1.05 95% CI 0.91, 1.21 I2=79%
Type of prior cancer	Mixed	7	1.24 95% CI 1.04, 1.49 I2=86%
	Head and neck	1	1.80 95% CI 1.07, 3.03
	Gastric	1	1.17 95% CI 0.71, 1.93
Treatment for lung cancer	Surgery	6	1.58 95% CI 1.25, 2.00 I2=65%
	Mixed	3	0.99 95% CI 0.85, 1.15 I2=68%

CI, confidence intervals.

cer in the same patient. One reason for such cases is the long-term effect of chemotherapy or radiotherapy used to treat first cancer leading to the development of future malignancies. Secondly, cancer-favoring lifestyle variables, environmental risk factors, and genetic predisposition can also contribute to the development of multiple primary cancers[23]. Indeed, the risk of prior extrapulmonary malignancies in the case of lung cancer patients ranges from 1 to 22%[18]. With such high numbers, clinicians are increasingly treating patients with multiple primary cancers without any concrete evidence of the prognostic significance of prior extrapulmonary malignancies.

In this meta-analysis, an attempt was made to answer this clinical query by pooling data from individual cohorts. On combining data from approximately 1.6 million patients, it was noted that prior extrapulmonary malignancy leads to a statistically significant 27% increase in the risk of poor OS, with a 95% CI ranging from 7% to 50%. Overall, all included studies individually demonstrated significantly poor OS or a tendency of poor OS in patients with a history of prior malignancies. Only one study by Aguiló et al[12] found that prior malignancy was associated with improved survival in lung cancer. The contrasting results of this study are difficult to explain and may be attributed to the limited sample size. Nevertheless, the stability of results on sensitivity analysis and lack of publication bias adds to the credibility of the review results.

The results of this review concur with data on other cancer subtypes. A recent study on 1,199 esophageal cancer patients with prior malignancy noted that prostate, breast, bladder, lung and bronchus, and larynx were the most common prior cancers in such patients; history of prior cancer was associated with significantly reduced cancer-specific survival (CSS)[24]. Similarly, Wen et al[25] in a study of 28,795 gastric cancer patients found that prior non-gastric cancer history is a significant factor for poor OS. However, they failed to note any impact on CSS. In another study, Zhu et al[26] noted similar results with larynx cancer wherein the prior history of other cancers reduced OS but did not lead to worse CSS. Contrastingly, not all studies have noted the negative impact of prior cancer on OS. Research has shown that prior cancer history is not a negative prognostic marker in hepatocellular cancer[27], intrahepatic cholangiocarcinoma[28], and pancreatic cancer[29]. Since individuals with prior cancers are often excluded in clinical trials, these results raise questions on such inclusion criteria and prompt reconsideration for future clinical trials. However, as our results suggest otherwise, we believe that the prognostic impact of prior cancer may vary with different cancer subtypes, and further research is needed on the impact of different variables on outcomes of lung cancer with prior cancer history.

Indeed, OS after lung cancer can be influenced by multiple variables and this was one important reason to include studies reporting only adjusted data in this meta-analysis. We also attempted multiple subgroup analyses and found that OS was influenced by prior cancer only in Asian studies but not in non-Asian studies. As the current number of studies was limited, there is a need for further research in this direction. Secondly, other important variables to consider are the type of prior cancer, stage of lung cancer, and treatment modality used. Comprehensive subgroup analyses for these factors could not be conducted due to a lack of data. However, a few studies[8,17] have presented some data for these variables. Monsalve et al[17] have shown that in stage I lung cancer, prior cancer history was associated with worse OS irrespective of the treatment modality used; while in the case of stage IV lung cancer, OS was better in patients with prior cancer history. Deng et al[8] in their study noted that prior cancer improved OS of lung cancer within one year of diagnosis and it decreased survival only

when the time interval to diagnosis was 5-10 years. In terms of different types of prior cancer, the same pattern was noted by the authors. Indeed, many such variables of valuable clinical significance are yet to be fully explored and only future studies with large sample sizes from different geographical regions can provide robust evidence.

Limitations

The results of our review should be interpreted with some limitations. Foremost of which is the observational and retrospective nature of data which can be prone to errors. In addition, the large bias occurring in management due to selection bias. Such bias can only be reduced by future propensity-score matched studies that take into account baseline variables. Secondly, most data was from limited countries which limit the applicability of outcomes to the entire global population. Thirdly, an extensive subgroup analysis was not possible taking into account multiple confounding variables due to the lack of data from included studies. Lastly, the review was focused only on OS, data on CSS and recurrence was scarce and hence could not be analyzed.

Strengths

However, the review has some strengths, and the results assume clinical significance. It is the first review on the subject and presents the only pooled analysis on the topic. The total sample size of the review was very large, and the results were stable on sensitivity analysis. We did not pool crude mortality data, and only adjusted data on OS was combined to add credibility to the results. Given the outcome of the review, it is suggested that lung cancer patients with prior history of extrapulmonary malignancies should be prioritized for treatment and patients should be adequately counseled regarding the impact of prior cancer on poor OS. Nursing personnel should provide high quality care to such patients owing to their tendency of poor outcomes. However, at the same time, further research should be conducted to identify specific factors affecting poor OS.

Conclusions

The result of this meta-analysis indicates that a history of prior extrapulmonary malignancy results in poor OS in patients with lung cancer. Caution is needed in the interpretation of the results owing to high interstudy heterogeneity. Further research is needed to assess how factors like the type of extrapulmonary malignancy, time interval of diagnosis, cancer stage, and treatment modality impact this relationship.

Authors' Contribution

HX conceived and designed the study, WC and CC collected data and performed data analysis. HX wrote the draft of this manuscript. YC edited the manuscript.

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Conflict of Interests

The authors declare that there is no conflict of interests.

Informed Consent and Ethics Committee approval

Not applicable

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