Associations between obstructive sleep apnea and the cardiac troponin T levels: A meta-analysis

Abstract

Objective: Cardiac troponin T (cTnT) is a sensitive indicator for heart damage and is an important clinical marker for acute myocardial infarction (MI). The recent development of a high-sensitivity cardiac troponin T (hs-cTnT) assay allows a more accurate diagnosis of C concentration. There appears to be an association between OSA and changes in serum cTnT levels. However, current research works in this area have reported mixed results. Therefore, this meta-analysis study was performed to evaluate the relationship between cTnT levels and OSA.

Method: The Scopus, Embase, Web of Science, PubMed and Science Direct databases were searched without a lower time limit and until April 2020. In order to perform the meta-analysis, the heterogeneity of articles was examined using the I^2 test, and subsequently a random effects model was applied. Data analysis was performed using the Comprehensive Meta-Analysis software (version 2).

Result: Six studies involving a total of 1,689 cases and 2,171 controls were included in this meta-analysis. The results of our study suggest that the aggregate odds ratio of hs-cTnT level in patients with OSA is 1.25 (95% confidence interval: 0.97-1.61).

Conclusion: Our findings indicate that patients with OSA have 25% higher rate of hs-cTnT levels than people without OSA.

Keywords: Obstructive Sleep Apnea; Cardiac Troponin T; Cardiovascular; Myocardial Infarction; Heart; Meta-Analysis.

Introduction

Obstructive sleep apnea (OSA) is a condition in which partial or complete obstruction of the upper respiratory tract occurs (Franklin and Lindberg, 2015; Senaratna et al., 2017); This obstruction may lead to intermittent hypoxia, hypercapnia, reoxygenation, cerebral blood flow, and sleep arousal (Emamian et al., 2016; Pugliese et al., 2020; Tahmasian et al., 2016). Factors that narrow throat during sleep, e.g. Obesity, increased throat and tongue fat, and swollen tonsils, can cause OSA (Kim et al., 2014). Moreover, both gender and age seem to impact the incidence of OSA, as studies show that the prevalence of OSA in older men is higher than other groups of people (Redline et al., 2010). The prevalence of this disease varies in different groups. For instance, the prevalence of OSA in women has been reported as 2-5%, whereas, this figure in the male population is 3-7% (Lindberg, 2010). Several studies demonstrated that OSA contributes to emotional and cognitive decline, and it has been considered as a variable risk factor for dementia (Emamian et al., 2016; Osorio et al., 2015; Polsek et al., 2018; Rosenzweig et al., 2015). In addition, daytime sleepiness, labile interpersonal relationships, lower work and school performance, higher rate of car accident, and poor quality of life have been reported as potential outcomes of OSA (Kasai et al., 2012; Khazaie et al., 2017; Leung and Douglas Bradley, 2001; Mohajer et al., 2020; Osorio et al., 2015).

Frequent airway obstruction leads to oxyhemoglobin unsaturation, CO2 retention, and decreased SaO2 levels (Redline et al., 2010). On the other hand, fluctuations in the cardiovascular autonomic activity are observed between the apneic and ventilatory phases in patients with OSA (Leung and Douglas Bradley, 2001). These complications prompt the release of inflammatory and prothrombotic mediators, activity increase of the sympathetic nervous system, and rise of free radicals and brain damage (Redline et al., 2010). Neuroimaging reviews and meta-analysis also pointed to structural and functional brain alterations in OSA (Khazaie et al., 2017; Mohajer et al., 2020; Tahmasian et al., 2016). OSA triggers the cardiovascular system, and this may lead to the onset or progression of cardiovascular diseases (CVD) (Kasai et al., 2012). The results of an existing research work reports that 50% of patients with metabolic and cardiovascular disorders have OSA (Tahmasian et al., 2016). Animal and human studies have shown that OSA induces intrathoracic pressure changes, which causes acute hemodynamic disturbances and results in adverse effects on left ventricular pressure and dimensions (Butt et al., 2010). Thus, OSA is recognized as an important risk factor for higher heart rate, hypertension, coronary artery disease (CAD), stroke, atrial fibrillation, and myocardial injury (Bradley and Floras, 2009; Khazaie et al., 2011).

Cardiac troponin (ctn) is a cardiac myofibrillar intracellular protein, which is used for the clinical diagnosis of heart disease and could be rapidly detected in blood after the myocardial injury. Hence, this protein is also considered as a special biomarker to diagnose acute coronary artery syndromes (Otsuka et al., 2010). The conventional measurement methods, can expose serum cTnT levels in only 1% of the general population. However, with the new high-sensitivity cTnT measurement method (i.e. hs-cTnT), serum cTnT levels can be detected in more than 97.7% of patients with coronary artery disease (Randby et al., 2012). Hs-cTnT can detect very small amounts of Troptonin T, and therefore has a higher sensitivity for the diagnosis of CAD compared to the conventional diagnostic methods such as ctni assays (Otsuka et al., 2010; Twerenbold et al., 2016; Zhang et al., 2018). Existing studies have demonstrated that the elevated hs-cTnT in serum is strongly associated with the side effects of hypertension such as CVD (Tehrani et al., 2019). However, the relationship between OSA and hs-cTnT levels is still unknown (Barceló et al., 2014). For instance, Sánchez-de-la-Torre et al have reported that serum hs-cTnT levels increase in patients with OSA (Sánchez-de-la-Torre et al., 2018). Nevertheless, other works have shown that cTnT levels are lower in patients with OSA at the time of a myocardial infarction, than in patients without OSA(Lin et al., 2018). Shah et al. argued that serum troponin T levels are significantly lower in patients with OSA, when facing myocardial infarction (Shah et al., 2013). Anatomical and functional changes in the myocardium, , depending on age and gender, are common factors in the development of OSA and increased troponin levels (Randby et al., 2012). Since different studies that had examined the relationship between obstructive sleep apnea (OSA) and cardiac cTnT levels reported dissimilar values of odds ratio, and as these values are inconsistent, this work intends to answer the following research question: what is the overall probability of having an increase in cardiac troponin T levels in patients with obstructive sleep apnea? Therefore, in order to find an answer to this question, this study was designed as a systematic review of the research works to examine the effect of obstructive sleep apnea and cardiac troponin T levels; a meta-analysis was also conducted to obtain the overall odds ratio of this relationship.

Method

Search Strategy

In order to conduct the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2015) guidelines,

we searched the Science Direct, Embase, Scopus, PubMed, Web of Science, and Google Scholar databases until April 2020. The keywords used for the search process include: Cardiac Troponin T[TIAB] OR Troponin T[MESH] OR CTNT [TIAB]OR TNT [TIAB] AND OSA[TIAB] OR Obstructive sleep apnea [MESH] OR Syndrome Obstructive sleep apnea [TIAB] OR OSA[TIAB]. In order to maximize the comprehensiveness of the search, the lists of references used within all the collected articles were manually reviewed. Duplicate articles that were collected from different databases were omitted, and only one copy was retained. No time limit was considered in the search process, and the meta-data of the identified studies were transferred into the EndNote reference management software (version X7, for Windows, Thomson Reuters).

Study Selection

The inclusion criteria were as follows: studies that have examined the association between cardiac troponin t levels and OSA, observational studies (non-interventional studies) , respiratory disturbance index (RDI) or apnea-hypopnea index (AHI) are used as the criteria for detecting apnea, and studies in which the apnea assessment tool was polysomnography. The exclusion criteria were follows (1) case reports, reviews, meta-analysis, or animal studies, (2) non-OSA studies (e.g. studies on sleep fragmentation or central sleep apnea), and interventional studies.

Initially, the title and abstract of the selected studies were examined by two reviewers (MM, SR) based on the inclusion and exclusion criteria. Subsequently, the full texts of the remaining articles were assessed according to the inclusion and exclusion criteria. All articles at this stage were in English or Persian. Throughout the articles review and examination processes, in case of disagreement between the two reviewers, the opinion of a third reviewer (NS) was taken into account as a criterion for inclusion (or exclusion) of an article. Among all the selected studies, OSA was measured by tools such as polysomnography, Apnea link Plus monitor and Cardiorespiratory Polygraph in accordance with AHI or RDI apnea measurement criteria. Moreover, observational studies that had reported odds ratios were also included. Finally, 6 studies entered the third stage i.e. quality evaluation.

Quality Evaluation

In order to evaluate the quality of the included studies, the STROBE checklist was used (Von Elm et al., 2007). STROBE checklists are commonly used to evaluate the quality of observational studies. The STROBE checklist consists of six scales/general sections including:

title, abstract, introduction, methods, results, and discussion. Some of these scales have subscales, and the total number of subscales/items is 32. These 32 items represent different aspects of the study such as title, problem statement, study objectives, study type, study statistical population, sampling strategy, and sample size, definition of variables and procedures, data collection methods, statistical analysis approaches, and findings. Accordingly, the maximum score that can be obtained using the checklist is 32. Considering the score of 16 as the cut-off point (Salari et al., 2020), articles with scores of 16 or above were considered as medium or high-quality articles. In this work, based on the evaluation conducted using the STROBE checklist, 6 medium or high-quality articles entered the systematic review and meta-analysis process.

Data Extraction

Details of all final articles that were included for the systematic review and meta-analysis process were extracted using a different checklist. The checklist included title of article, first author's name, year of publication, place of study, sample size, BMI (kg/m^2), AHI (event s/h), Cardiac Troponin T, study type, and mean age of patients and controls.

Statistical Analysis

The I^2 test was used to evaluate the heterogeneity of the selected research works. In order to investigate publication bias, due to the high volume of samples entered into the study, the Egger's test was used at the significance level of 0.05, and the corresponding Funnel plots were drawn. Data analysis was performed within the Comprehensive Meta-Analysis software (version 2).

Results

The method of collecting and selecting eligible studies is presented in Figure 1. A total of 498 articles were collected following an initial search of the above-mentioned databases. Among these articles, 112 duplicate studies were excluded, and the remaining 386 articles were examined. Subsequently, 279 articles were omitted after reviewing their titles and abstracts. After reviewing the full text of the remaining articles, another 101 articles were excluded, and 6 articles were finally approved, and entered into the meta-analysis process.

(Figure 1 here)

After evaluating the 6 observational articles included in the present study, it was clear that 5 articles were cross-sectional (Geovanini et al., 2016; Kohno et al., 2017; Randby et al., 2012; Roca et al., 2015; Roca et al., 2013), and the other research work was performed using the cohort method (Shah et al., 2013). The final collected studies were published between 2012 and 2018. Three of these works were conducted in the United States (Roca et al., 2015; Roca et al., 2013; Shah et al., 2013) and the other studies had taken place in Japan (Kohno et al., 2017), Brazil (Geovanini et al., 2016) and Norway (Randby et al., 2012). The samples in 2 studies were hospitalized patients (Kohno et al., 2017; Shah et al., 2013). One study examined patients referred to a heart clinic (Geovanini et al., 2016) and another work selected the sample from a sleep laboratory (Randby et al., 2012). The remaining two studies selected their sample from the study population in the ARIC cohort conducted in the United States between 1987-1989 (Roca et al., 2015; Roca et al., 2013).

Different tools were used to measure OSA. In 4 studies, the OSA pattern was measured using polysomnography (PSG) (Geovanini et al., 2016; Randby et al., 2012; Roca et al., 2015; Roca et al., 2013), and another research work measured OSA using the Apnealink Plus monitor (Shah et al., 2013). The final remaining study measured the changes in pressure using a pressure transducer and changes in oxygen levels using pulse oximetry to diagnose the occurrence of apnea or hypopnea in OSA (Kohno et al., 2017). According to the current guidelines, AHI ≥ 5 / h is considered as a measure of OSA (Eiseman et al., 2012); however in 4 of the selected studies, this criterion (AHI > 5) was considered as an indication of OSA (Kohno et al., 2017; Randby et al., 2012; Roca et al., 2015; Shah et al., 2013), whereas, in one other study, a different criterion (i.e. AHI> 15) was used and this difference in the use of OSA indication criteria was due to the high prevalence of OSA among the study patients with RA (Geovanini et al., 2016). In the only remaining study, OSA incidence was diagnosed through RDI (Roca et al., 2013), in which 'RDI > 5' was considered as OSA.

Since the cTnT detection in a patient's bloodstream is often associated with cardiovascular disorders, in all but one study (Randby et al., 2012), the subjects had cardiovascular complications. Accordingly, in one research work, the sample consisted of patients with acute myocardial infarction (Shah et al., 2013). In another work, patients with myocardial injury due to refractory angina were evaluated (Geovanini et al., 2016). The study of Kohno et al. examined patients with pulmonary hypertension (Kohno et al., 2017). In the last two works,

patients with heart failure and coronary heart disease were examined (Roca et al., 2015; Roca et al., 2013).

The time for collecting serum cTnT concentration samples (for testing) was also different in the studies; two research works took the patient's blood sample after PSG (Geovanini et al., 2016; Randby et al., 2012). In one work, patients were sampled at 72 hours after the onset of MI symptoms, at regular intervals; in the same work, the highest cTnT concentration was selected as the sample (Shah et al., 2013). In the other two studies, blood samples were taken from patients at the early stages of the research works (Roca et al., 2015; Roca et al., 2013). The time and method of sampling in the study of Kohno et al. was not clear (Kohno et al., 2017) (Table 1).

(Table 1 here)

Within the final collected studies, a total of 4,050 people had been surveyed, of which 1,689 in the OSA group and 2,171 in the without OSA. The lowest and highest numbers of patients with OSA were 16 and 745 respectively, and the numbers in the control group ranged between 20 and 910. As reported in Table 2, the age range of the samples was between 52.75 and 64.06. The mean age of the studied population was 57.5 years, and 46.9% of the samples were male. Furthermore, the prevalence of hypertension, hyperlipidemia, and diabetes in the studied samples were 77%, 56%, and 50% respectively. Considering the distribution of variables related to demographic factors, with the exception of age and BMI, the statistical correlation between OSA and non-OSA groups was significant. The BMI of the OSA group was higher than the non-OSA group, and the age of patients with OSA was significantly higher than the age of non-OSA patients. The average AHI was 5 in the OSA group and 1 in the non-OSA group. The oxygen saturation index (ODI) was higher in the OSA group and was strongly associated with AHI. There was no statistically significant difference between the two groups in terms of Epworth score or average oxygen saturation (throughout the night). Furthermore, there was no significant difference between the OSA and non-OSA groups in terms of percentage of sleep time and the oxygen saturation of less than 90%. In the unadjusted analysis, acute MI patients with OSA had a lower mean Peak Troponin than patients without OSA. In this study, higher AHI was associated with lower levels of cTnT and it was predicted that for each unit of increase in AHI, there was an 8% reduction in the high levels of cTnT.

(Table 2 here)

Assessing heterogeneity and publication bias

The heterogeneity of the studies was investigated using the I^2 test. The obtained I^2 score was 92.06% denoting a high level of heterogeneity in the collected research works. The overcome this, the model of random effects was used to amalgamate the results of studies. Moreover, the existence of publication bias was evaluated using the Egger's test (Figure 2), and the result was not statistically significant (P = 0.476).

(Figure 2 here)

According to the meta-analysis conducted on the reported results of the 8 final studies, the odds ratio of heart troponin T in people with OSA was 1.25 (95% confidence interval: 0.97-1.61), meaning that patients with obstructive sleep apnea are 25% more likely to have a higher hs-cTnT levels, compared to people without OSA. Figure 3 illustrates the odds ratio that was calculated based on the random effects model, in which the black square represents the odds ratio and the length of the line, on which the square is located, denotes the 95% confidence interval in each study. The diamond shape represents the odds ratio calculated for all studies combined.

(Figure 3 here)

Discussion

The present study is the first meta-analysis performed to investigate the relationship between OSA and the serum hs-cTnT concentration. The results of this study show that the odds ratio of increasing serum hs-cTnT concentration in patients with OSA compared to the control group is 1.25. In other words, the serum concentration of hs-cTnT is 25% higher in patients with OSA. It was also observed that with increasing age and BMI, hs-cTnT levels increases in both groups with or without OSA.

Epidemiological studies indicate that OSA has a negative effect on cardiovascular system as a result of various mechanisms. It is also argued that OSA is associated with the prevalence and progression of CVD (Lu et al., 2020; Yaggi et al., 2005). Moreover, OSA is strongly associated with metabolic disorders such as obesity, hypertension, dyslipidemia, and glucose metabolic diseases. Therefore, this disease can be considered as a key risk factor for CVD (Li et al., 2020). On the other hand, increasing the level of various biomarkers such as oxidative stress, adhesion molecules, chemokines and cytokines due to OSA, can elevate the risk of CVD (Williams and Scharf, 2007). Injuries such as necrosis and apoptosis in myocytes can also increase cTnT in the bloodstream (Koide et al., 2010).

CTnT is a very sensitive and specific marker for myocardial necrosis and is considered as a predictor of CAD side effects. This marker also increases in other diseases such as renal failure. However, the mechanisms affecting the increase in cTnT levels are still unclear (Han et al., 2009). Otsuka et al. Reported that increased serum hs cTnT concentrations are associated with several CVD risk factors. According to the results of their research work, the CVD risk odds ratio in the comparison between the highest value of hscTnT (≤ 0.005) ng/m and the lowest value measured in the work (≥ 0.002 ng/ml) was 3.98. It was also observed that high levels of hs-cTnT can be considered as a predictor of CVD risk in middle-aged men, with or without a history of CVD (Otsuka et al., 2010). The study by Seung Hyeok et al. Also demonstrated that the survival of patients with CVD decreases with increasing hs cTnT (Han et al., 2009). The present study shows that OSA is associated with an increase in serum hscTnT. Therefore, it can be concluded that increasing the concentration of hs cTnT is one of the effective factors in the incidence of CVD in the OSA patients (Figure 4).

(Figure 4 here)

The role of OSA in increasing the risk CAD development in existing literature provides mixed and inconsistent results. A study examining the role of OSA in the incidence of myocardial injury in patients with refractory anginam, conducted sampling in 4 occasions in every 24 hours. This study showed that in patients with severe OSA, serum hs-cTnT levels are higher in the morning than in the other sampling sessions. However, these changes were not observed in people with mild and moderate OSA (Geovanini et al., 2016). Although some studies, such as our study, have suggested that OSA is associated with cardiovascular clinical morbidity and mortality, another research work argues that patients with OSA, especially severe OSA, experience less heart damage. According to this work, in fact, OSA plays a protective role against myocardial damage (Sánchez-de-la-Torre et al., 2018). Another study found that people with OSA are less likely to suffer from acute heart damage. And severe OSA can have a protective effect in the acute stage of myocardial infarction (Shah et al., 2013). Another piece of research demonstrated that patients with OSA suffer from CAD as well. They have no signs of myocyte necrosis that can be measured by hscTnT. In fact, this study showed that cTnT is not detectable in the serum of patients with CAD, who suffer from moderate to severe OSA (Gami et al., 2004).

Based on a population-based study, age and gender cause differences in hs cTnT concentrations (DeFilippi et al., 2010). Another piece of research reported that cTnT concentrations are higher

in the elderly and men than others. This study also showed that cTnT concentration increases sharply in people over 60 years old (Welsh et al., 2018). As mentioned earlier, obesity is one of the effective factors in increasing hscTnT concentration. According to the results of a study conducted in 2014, an increase in BMI is associated with a positive and linear increase in hscTnT concentrations. Severe obesity (BMI> 35 kg/m2) was also reported to increase hscTnT 2.02 (Ndumele et al., 2014).

In addition to the clinical significance of the results obtained in our work, it is also important to investigate the mechanism of CVD in OSA patients. The main characteristic of OSA is the recurrence of nocturnal hypoxia. It seems that such hypoxic events have an influence in the occurrence of cardiovascular injuries (Collinson et al., 2001). OSA-related stressors such as negative intrathoracic pressure swings, sleep fragmentation, and sympathetic activation contribute to OSA-related cardiovascular pathophysiology. With sympathetic system activation and vasoconstriction, the sympathetic response to hypoxia is weakened by stretching of the thoracic afferents. As a result, apnea and the absence of chest inflation increase the effect of hypoxic sympathetic vessels (Dewan et al., 2015). An animal study hasdemonstrated a strong correlation between serum cTnT levels during hypoxia and oxidation. This study also showed that there is no maximum limit for serum cTnT level during hypoxia and oxidation (Asayama et al., 1992).

Limitation and recommendation

Our work is not without limitations; most of the selected studies were cross-sectional, based on which the results cannot be examined longitudinally and over time. Moreover, there are two further limitations: This meta-analysis examined a small number of research works which may impact the generalisation of our findings. Furthermore, none of the articles generated results based on ethnicity. This meta-analysis showed that various risk factors such as age and BMI can play a role in the development of OSA as well as an increase in troponin T concentrations. On the other hand, it was stated that OSA is also effective in increasing the concentration of troponin T. Thus, as a future work, we can examine the relationship between ethnicity, OSA and troponin levels, as well as the effects of various related risk factors within the context.

Conclusion

This study demonstrated that OSA patients have a higher chance of having an increase in cTnT, and that moderate to severe OSA is associated with an increase in Hs-tnt levels. In other words, OSA is indirectly associated with higher hs-tnt levels. It has also been reported that the OSA severity is independently associated with cTnT levels. It was also argued that age and BMI could increase the serum concentration of troponin T in the case and control groups. This means that aging and obesity increase the risk factors for CVD, especially myocardial injury.

Table 1: Demographic information of studies reviewed in the meta-analysis

Author, Year	Country	Average age		Type of study	Source	Comorbidities	Sleep apnea assessment	Cutoff for AHI	Blood drawing times
		OSA	Control						
Neomi Shah, 2013(Shah et al., 2013)	America	62	52	Cohort	Inpatient / outpatient	MI acute patients	Apnea link Plus monitor	>5	Within 72 h of presentation with symptoms of MI
Takashi Kohno, 2017(Kohno et al., 2017)	Japan	63.9	52.6	Cross sectional	Inpatient / outpatient	PH	Pressure transducer and pulse oximetry	>5	Not mentioned
Glaucylara R Geovanini, ,2016(Geovanini et al., 2016)	Brazil	63	59	Cross sectional	Inpatient / outpatient	RA	PSG	>15	After PSG
Anna Randby, 2012(Randby et al., 2012)	Norway	52.75	44	Cross sectional	Inpatient / outpatient	_	PSG	>5	The morning after PSG
Gabriela Querejeta Roca, 2015.(Roca et al., 2015)	America	64.06	63.5	Cross sectional	_	CHD and HF	PSG	>5	Time of ARIC visit
Gabriela Querejeta Roca, 2013. (Roca et al., 2013)	America	63.02	61.06	Cross sectional	_	CHD and HF	PSG	RDI, >5	Time of ARIC Visit

AHI: Apnea–Hypopnea Index, RDI: Respiratory Disturbance Index, PSG: Polysomnography, CRP: Cardiorespiratory Polygraphy, ACS: Acute Coronary Syndrome, MI: Myocardial Infarction, PH: Pulmonary Hypertension, RA: Refractory Angina, CHD: Coronary Heart Disease, HF: Heart Failure, ARIC: ARIC is a prospective epidemiologic cohort study that enrolled 15,792 middle-aged subjects between 1987 and 1989

Table 2: Characteristics of the included studies in the meta-analysis

Author	OSA subjects					Control subjects					OR	Confidence interval	P value
	Age(mean)	BMI (mean)	No. (Male)	AHI (events /h)	TNT	Age(mean)	BMI (mean)	No. (Male)	AHI (events /h)	TNT			
Neomi Shah (2013)	62	30	47 (20)	5	1.02	52	27	31 (20)	1	1.72	0.918	0.856-0.984	0.0151
Takashi Kohno (2017)	63.9	NR	16 (4)	21.25	13	52.6	NR	81 (16)	3.4	6	0.763	0.436-1.090	<0.001
Glaucylara R Geovanini(2016)	63	30	60 (42)	41	40	59	27	20 (11)	26	25	4	1.17-13.73	0.028
Anna Randby(2012)	52.75	30.7	280 (183)	30.8	53.2	44	27.4	225 (95)	1.5	29.8	1.032	1.020-1.043	<0.001
Gabriela Querejeta Roca(2015)	64.06	30.6	440 All men	NR	1.05	63.5	27.5	312 All men	NR	NR	1.48	1025-1.74	<0.001
Gabriela Querejeta Roca(2015)	62.96	33.3	301 (0)	NR	1.42	61.4	26.8	592 (0)	NR	NR	1.20	1.04-1.37	0.01
Gabriela Querejeta Roca(2013)	63.63	31.6	745 (443)	NR	0.005	61.8	27	910 (315)	NR	0.004	1.45	1.32-1.60	0.007

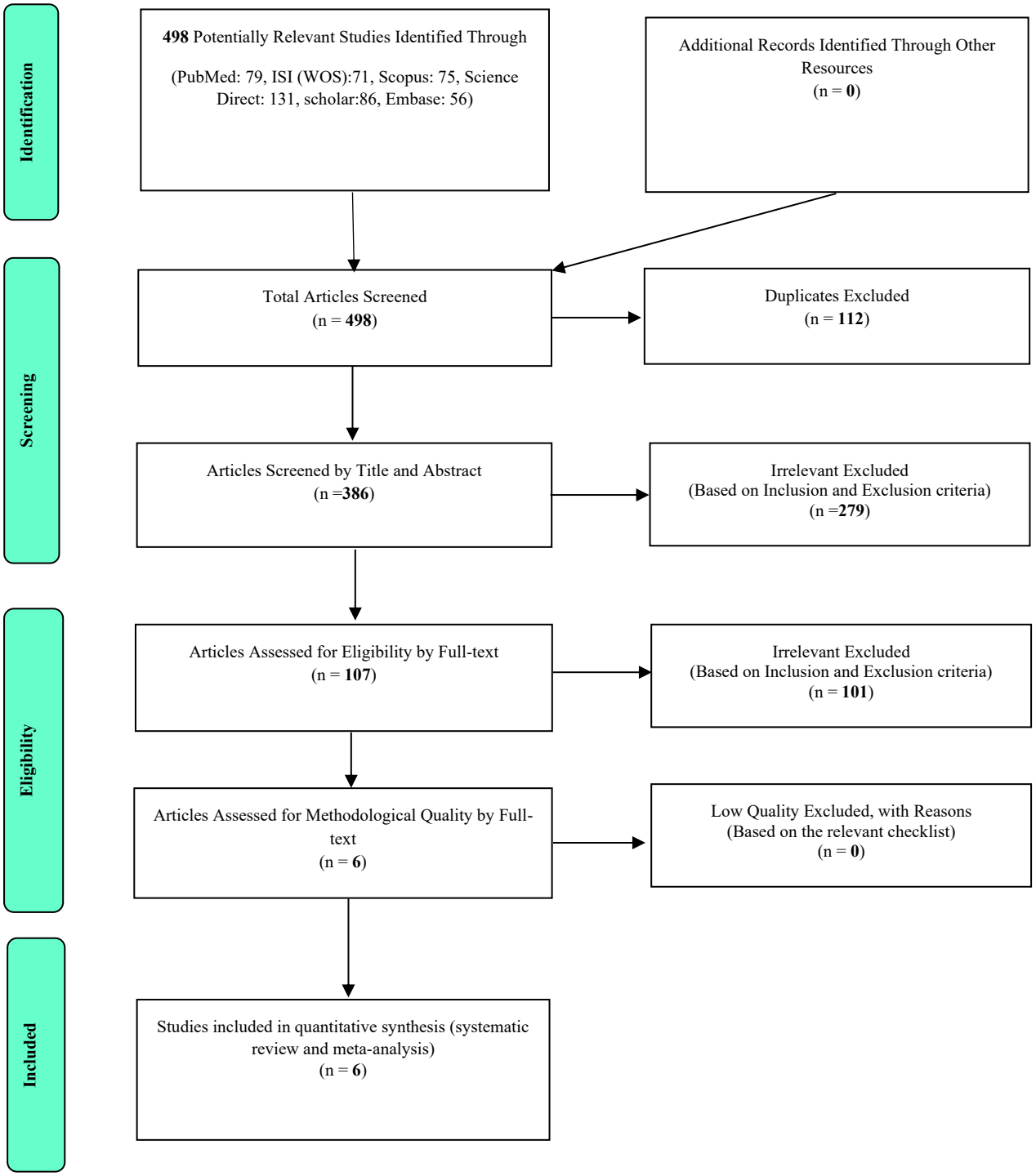

Figure 1: of the PRISMA flow diagram demonstrating the process for including studies in the systematic review and meta-analysis.

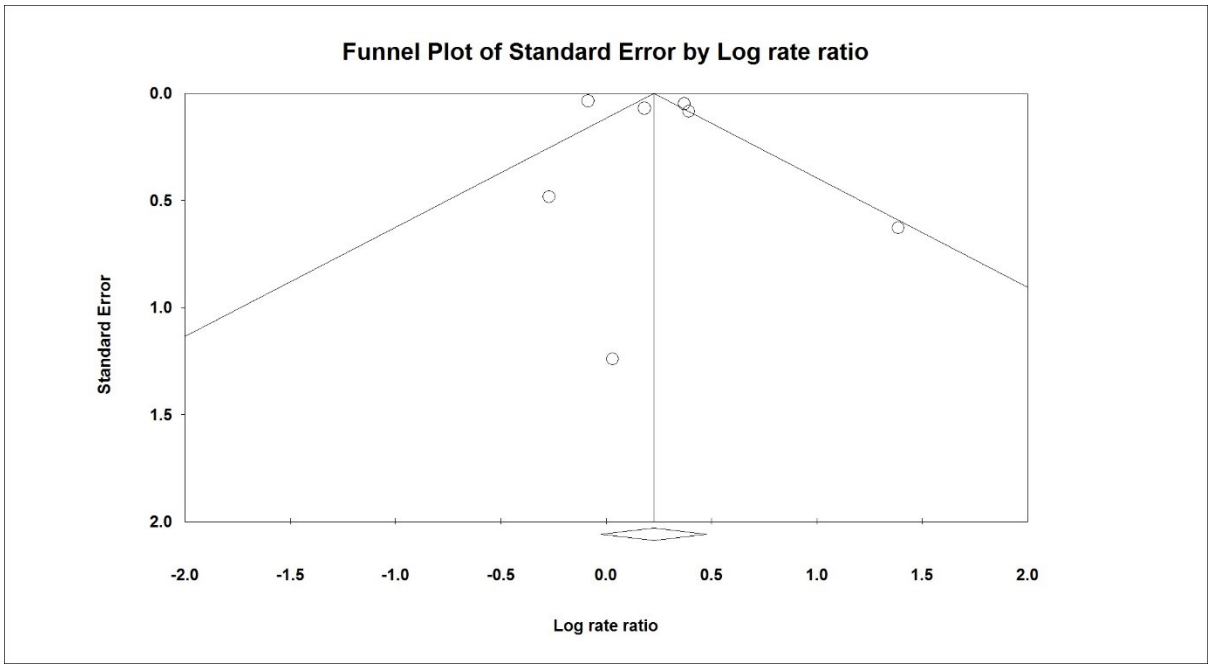

Figure 2: Funnel Plot Results for Troponin T Heart Rate and OSA.

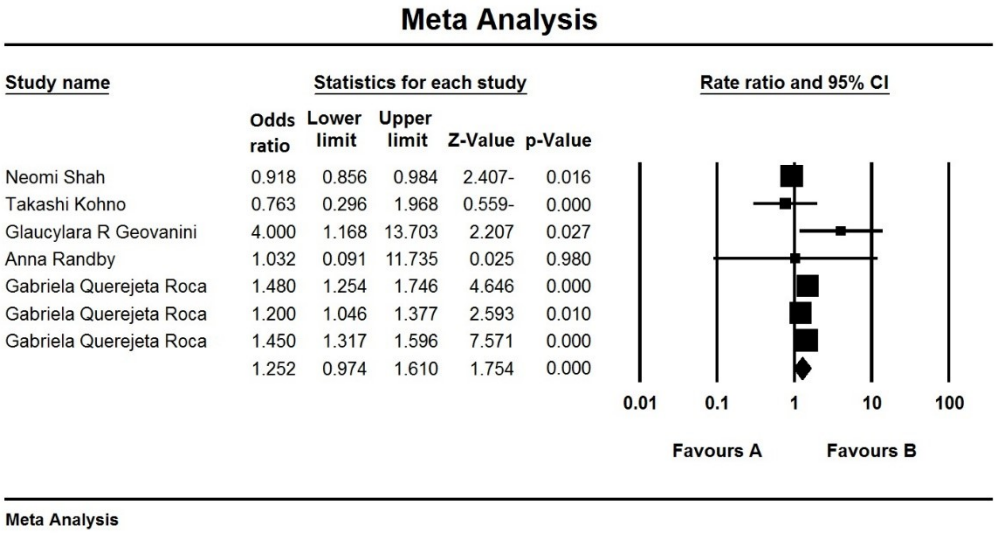

Figure 3: The odds ratio of heart troponin T levels in people with OSA and based the model of random effects.

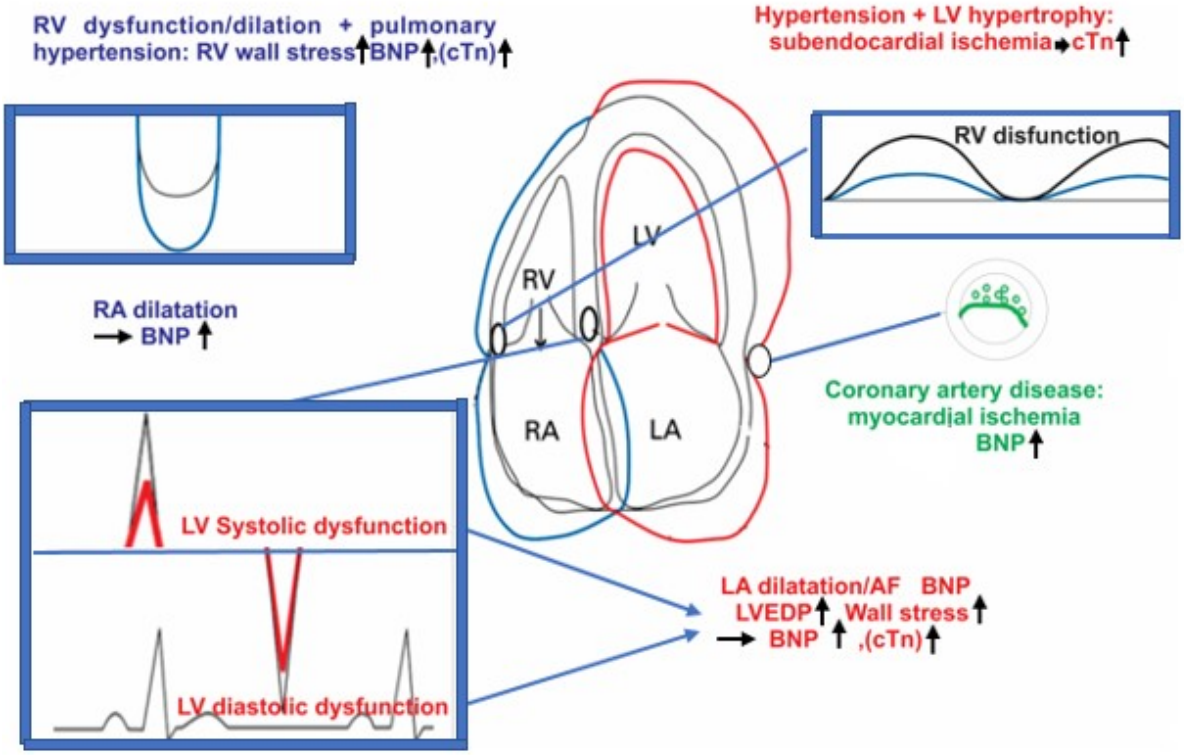

Figure 4: Schematic representation of the cardiac effects of obstructive sleep apnea (OSA) and the mechanism leading to the release of B-type natriuretic peptide (BNP) and cardiac troponin (ctn) from heart. Blue: right heart and pulmonary circulation, red: left heart and systemic circulation, green: coronary arteries. AF: atrial fibrillation, LA: left atrium/atrial, LV: left ventricle/ventricular, RA: right atrium/atrial, RV: right ventricle/ventricular.

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