



Brief Report

Risk of Obstructive Sleep Apnea in Adults with Resistant Hypertension

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Abstract: The risk of obstructive sleep apnea (OSA) in patients with resistant hypertension (RH) has not been well-quantified. We sought to evaluate the risk of OSA in patients with RH compared to those with treated but non-resistant hypertension (non-RH) using a time-dependent-exposure analysis. We conducted a retrospective cohort study of patients with treated hypertension (hypertension diagnosis + ≥ 2 antihypertensive drug claims within 1 year) using the IBM MarketScan[®] commercial claims database from January 2008 to December 2019. We excluded patients without 12 months of continuous enrollment before the second antihypertensive fill date (index date of cohort entry) and those having the outcome (OSA) in the 12-month pre-index period. We employed Cox proportional hazard regression with OSA as the dependent variable, and time-dependent exposure (non-RH vs. RH) and baseline covariates as independent variables. Of the 1,375,055 patients with treated hypertension, 13,584 patients were categorized as exposed to RH. In the multivariable Cox proportional hazards model, exposure with RH was associated with a 60% increased risk of OSA (adjusted hazard ratio (aHR): 1.60; 95% CI, 1.52–1.68) compared to non-RH exposure. Findings of the study suggest that exposure with RH, compared to non-RH, is associated with a higher risk of incident OSA.

Keywords: resistant hypertension; sleep apnea; antihypertensives



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1. Introduction

Resistant hypertension (RH) is defined as uncontrolled blood pressure despite treatment with four or more antihypertensive medications including an angiotensin-converting enzyme inhibitor, diuretic, β -blocker, or calcium channel blocker [1]. Obstructive sleep apnea (OSA) is one of the most common forms of sleep disorder, characterized by recurrent episodes of upper-airway closure leading to intermittent hypoxia and sleep fragmentation. Epidemiologic data suggest there may be a causal, bidirectional relationship between OSA and RH [2,3]. Intermittent hypoxia in OSA increases oxidative stress, metabolic dysregulation, and systemic inflammation, leading to renin-aldosterone activation as well as endothelial dysfunction, suggesting that OSA is an independent cause of resistant hypertension [2,3]. Conversely, excess aldosterone in RH increases the volume overload, causing blockage of the upper-airway muscles and intermittent hypoxia (OSA), thus suggesting a bidirectional relationship [2,3].

Although prior studies have identified OSA as a risk factor for RH, data regarding the risk of OSA in patients with RH are scarce. Bhandari and colleagues conducted a retrospective cohort study using data from Kaiser Permanente, an integrated health system [4]. They concluded that patients with RH are 16% more likely to develop OSA compared to patients with non-RH. However, this study was limited by use of a time-fixed

(i.e., time-independent) definition of RH and was also subject to immortal time bias and unmeasured confounding. Thus, it is still not clear to whether and what extent patients with an exposure to RH have a higher risk of incident OSA compared to non-RH exposure. Thus, we sought to evaluate the risk of OSA in a sample of patients with treated hypertension in the US comparing RH and non-RH exposure.

2. Results

2.1. Patient Baseline and Clinical Characteristics

Our initial sample consisted of 16,732,799 patients with at least two antihypertensive prescription claims within a year between January 2008 and December 2019. From this sample, we excluded patients without 12-months continuous medical and pharmacy enrollment before the cohort entry ($n = 10,170,961$), patients without a history of hypertension ($n = 5,068,157$), patients under 18 years old at the cohort entry date ($n = 6,246$), and patients with a diagnosis of OSA in the baseline period ($n = 112,380$). Our final cohort consisted of 1,375,055 patients meeting the definition for “treated hypertension.” Table 1 describes the baseline characteristics of the cohort. The mean age was 50 years, and 50.6% patients were men. The majority of patients were aged 51–64 years (54.5%) and resided in the southern region of the United States (48.7%). Obesity (11.5%) and hyperlipidemia (41.3%) were the most common comorbidities, whereas antidepressants (19.6%) and opiates (27.6%) were the most common prescription medications used during the baseline period. The mean (SD) Quan–Charlson comorbidity score was 0.5 (1.1). Overall, the most commonly filled antihypertensive medications were beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and calcium channel blockers in RH and non-RH groups.

Table 1. Baseline characteristics of treated hypertension patients.

Baseline Characteristics	N = 1,375,055
Demographics	
Age, years	
18–35	120,153 (8.7)
36–50	481,273 (35.0)
51–64	749,053 (54.5)
≥65	24,576 (1.8)
Sex	
Male	696,107 (50.6)
Female	678,948 (49.4)
Region	
Northeast	234,326 (17.0)
North Central	287,157 (20.9)
South	669,285 (48.7)
West	178,434 (13.0)
Unknown	5853 (0.4)
Medical history	
Quan–Charlson comorbidity score	0.5 (1.1)
Asthma	66,033 (4.8)
Obesity	158,147 (11.5)
Heart Failure	22,599 (1.6)
Hyperlipidemia	567,807 (41.3)
Anemia	40,432 (2.9)
Depression	109,859 (8.0)
Anxiety	134,332 (9.8)
Coronary artery disease	87,698 (6.4)
Stroke	19,552 (1.4)
Migraine	44,047 (3.2)
Transient ischemic attack	12,966 (0.9)
Substance use disorder	47,703 (3.5)
Chronic Kidney Disease	22,301 (1.6)

Table 1. Cont.

Baseline Characteristics	N = 1,375,055
Medication history	
Antidiabetic	166,362 (12.1)
Antihistamines	105,062 (7.6)
Antidepressants	269,393 (19.6)
Anticonvulsants	76,469 (5.6)
Antipsychotic	18,014 (1.3)
Barbiturates	553 (0.04)
Benzodiazepines	159,334 (11.6)
Opiate	379,038 (27.6)
Healthcare resource utilization	
Number of outpatient visits	12.0 (12.1)
Number of inpatient visits	0.8 (4.4)

Note: Data are presented as mean $\pm$ standard deviation (SD) or n (%).

2.2. Classification of RH and Non-RH Exposures

Of 1,375,055 patients with treated hypertension, 13,584 patients met RH at some point during follow-up. The mean duration of follow-up was 762 days RH exposure and 854 days for non-RH exposure. We identified 1532 incident OSA cases in during RH exposure and 93,397 incident OSA cases during non-RH exposure.

2.3. Risk of OSA

The crude incidence rates of OSA were 54.0 and 29.0 per 1000 person-years for RH exposure and non-RH exposure, respectively. The Kaplan–Meier survival curve (Figure 1 indicated that patients with RH exposure had a higher risk of OSA with significant log-rank test results ($p < 0.0001$) in crude analysis. In the multivariable Cox proportional hazards model adjusted for demographics (age, sex, region), clinical comorbidities (Quan–Charlson comorbidity score, asthma, obesity, heart failure, anemia, depression, anxiety, hyperlipidemia, stroke, migraine, chronic kidney disease, coronary artery disease, transient ischemic attack, substance use disorder), prescription-medication utilization (antidiabetics, antihistamines, antidepressants, anticonvulsants, antipsychotics, barbiturates, benzodiazepines, and opioids) and healthcare resource utilization (number of outpatient visits, and number of inpatient visits), compared to non-RH, RH exposure incurred a 60% increased risk of OSA (adjusted hazard ratio (aHR): 1.60; 95% CI, 1.52–1.68) (Table 2).

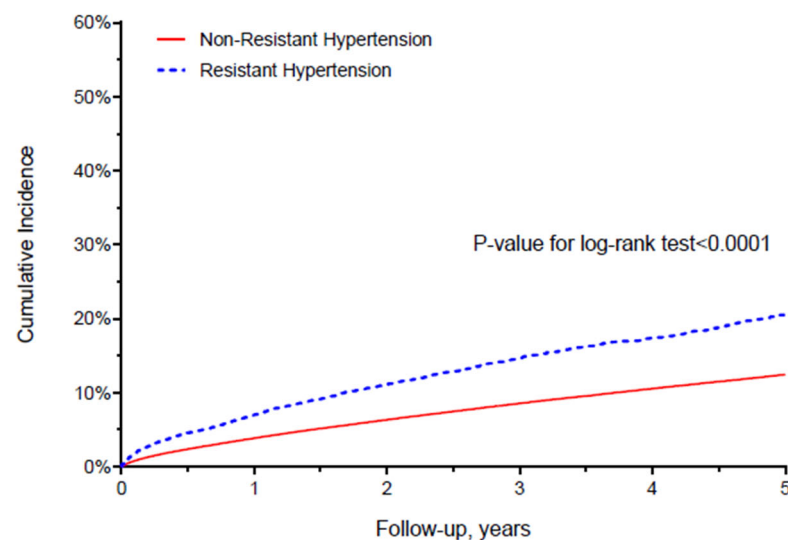


Figure 1. Kaplan–Meier curves for cumulative incidence of OSA among patients with and without resistant-hypertension exposure.

Table 2. Risk of obstructive sleep apnea (OSA) among patients with resistant hypertension and non-resistant hypertension.

Primary Outcome: OSA	Resistant Hypertension	Non-Resistant Hypertension
N	13,584	1,375,055
No. of OSA events, n	1532	93,397
Days of follow-up, mean	762	854
Person-years	28,381	3,217,461
Incidence rate per 1000 person-years	53.98	29.02
Unadjusted hazard ratio (95% CI)	1.73 (1.65, 1.82)	Reference
Adjusted hazard ratio * (95% CI)	1.60 (1.52, 1.68)	Reference

* Adjusted for age, sex, region, Quan–Charlson comorbidity score, asthma, obesity, heart failure, anemia, depression, anxiety, hyperlipidemia, stroke, migraine, chronic kidney disease, coronary artery disease, transient ischemic attack, substance use disorder, antidiabetics, antihistamines, antidepressants, anticonvulsants, antipsychotics, barbiturates, benzodiazepines, opioids, number of outpatient visits, and number of inpatient visits.

3. Discussion

To the best of our knowledge, this is the largest study to date to examine the risk of OSA associated with RH compared to non-RH. Our principal findings suggest that RH exposure was associated with a 60% increased risk of OSA compared to non-RH. The results from this study provide a novel contribution to the literature by quantifying the risk for development of incident OSA in patients with and without RH exposure.

Although OSA is an important public health concern and is highly prevalent in the US, OSA is underrecognized and underdiagnosed in the RH population [5]. Inadequate treatment of OSA with continuous positive-airway-pressure therapy can not only lead to uncontrolled blood pressure in patients with RH [6] but also to unnecessary treatment intensification with an additional antihypertensive, thus increasing the risk of hypotension and other severe adverse effects. Given the high clinical and financial burden associated with OSA for payers and patients/families [7], such findings may provide insights on the further development of strategies and policies to facilitate screening and regular monitoring of OSA among patients with RH.

A major strength of this study is the use of a large, diverse population and being representative of commercially insured adults in the U.S. Additionally, the mean follow-up time was more than 2 years. Therefore, we could assess the longer-term risk of OSA in patients with and without RH. Despite these strengths, this study has some limitations. First, we used a sample of commercially insured individuals, with possibly limited generalizability to Medicaid and Medicare populations. Second, we did not have access to polysomnography laboratory results and therefore relied on ICD-9-CM and ICD-10-CM diagnosis codes to identify patients with OSA, which may have introduced misclassification. However, since we used the same outcome definition for the exposure groups (i.e., RH and non-RH), any misclassification is likely to be non-differential and likely to bias results to the null. Third, because this is an observational study, it may be susceptible to residual confounding.

4. Materials and Methods

4.1. Data Source

We conducted a retrospective cohort analysis using IBM MarketScan® commercial claims database from January 2008 to December 2019. This database consists of nationwide administrative claims data over 180 million beneficiaries and their dependents covered under a variety of health benefit plans [8]. This database is representative of ≈49% of the US population receiving health insurance under employer-sponsored programs.

4.2. Study Population

The study population consisted of adults (≥18 years old) who had at least two antihypertensive prescription drug claims within a calendar year from January 2008 to December 2019. We required evidence of a second prescription fill to ensure that patients were treated

for hypertension. To avoid immortal time bias, patients entered the cohort on the date of the second antihypertensive refill date (i.e., index date of cohort entry) after a 365-day period of continuous medical and pharmacy enrollment (i.e., baseline period). During the baseline period, patients were required to have at least one inpatient or two outpatient diagnosis code for hypertension (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 401.x; International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM): I10.x). Patients with a diagnosis of OSA (the outcome) in the baseline period were excluded.

4.3. Exposure Definition

To assess the association between exposure to RH and the risk of developing OSA, a time-dependent exposure analysis was performed. Exposure was classified as non-RH (treatment with ≤ 3 antihypertensive drugs concurrently) or RH (treatment with ≥ 4 antihypertensive drugs concurrently for at least 60 days) [9]. Patients meeting RH criteria were considered to have RH indefinitely thereafter. The 60-day period was chosen to ensure persistent, concurrent use of ≥ 4 antihypertensive drug classes. The first day of overlapping use of ≥ 4 antihypertensive drugs for at least 60 days was defined as the index date for the RH exposure.

4.4. Study Outcome and Follow up

The primary outcome of interest was OSA identified by requiring at least one inpatient hospital discharge or two outpatient visits on different days with a qualifying diagnosis of OSA in any position using ICD-9-CM (780.51, 780.57, 780.53, 327.23; or ICD-10-CM (G47.30, G47.33, G47.39) codes. The earliest date of diagnosis of OSA was identified as the date of outcome.

All patients entered the cohort on the day of second prescription fill of antihypertensives (i.e., index date). Patients were followed from the index date until the earliest of first occurrence of: the outcome, end of continuous medical and pharmacy enrollment or the study end date (31 December 2019). For patients meeting RH criteria, exposure was classified as non-RH until the RH definition was met, and as RH thereafter, whereas for those never meeting RH criteria, all follow-up time was classified as non-RH (Figure 2a,b).

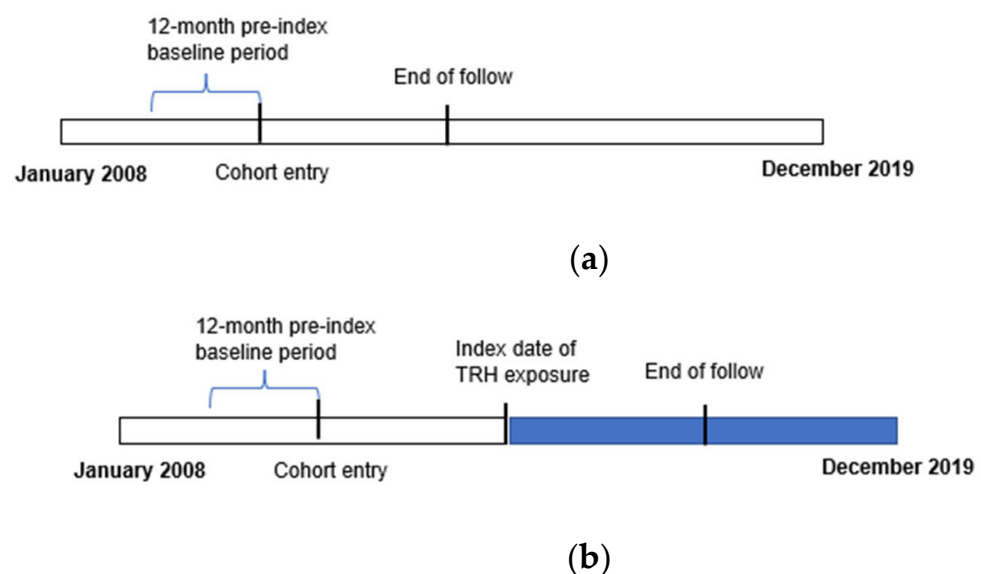


Figure 2. Study Design. (a) For the non-RH patients, the person days of follow-up were classified as non-RH (white); (b) For the RH patients, the person days of follow-up were classified as non-RH (white) until RH definition was met, and as RH thereafter (blue).

4.5. Baseline Covariates

Potential confounders were identified through a literature review and measured during the baseline period, including the index date. We assessed demographic characteristics (i.e., age, sex, region) and specific comorbidities of interest (i.e., asthma, obesity, heart failure, anemia, depression, anxiety, hyperlipidemia, stroke, migraine, chronic kidney disease, coronary artery disease, transient ischemic attack, and substance use disorder). Additionally, to better account for potential confounding by other comorbidities, we also measured the Quan–Charlson comorbidity index score (calculated based on the presence of ICD-9-CM and ICD-10-CM diagnosis codes) which includes 17 comorbidities [10]. We also assessed prescription medication use (i.e., antidiabetics, antihistamines, antidepressants, anticonvulsants, antipsychotics, barbiturates, benzodiazepines and opioids) and healthcare utilization patterns (i.e., number of outpatient visits and number of inpatient hospital visits).

4.6. Statistical Analysis

We conducted descriptive analysis of categorical variables and reported numbers and percentages. The incidence rate of OSA was calculated as the number of OSA events divided by the observed time at risk, expressed per 1000 person-years. A Kaplan–Meier curve was generated to visualize the OSA risk over time between the RH and non-RH patients, and its significance was tested using the Log-rank test. A Cox proportional hazards model with time-varying exposure (RH vs. non-RH) was used to compare the risk of developing OSA in RH patients compared with non-RH patients, adjusting for potential confounders. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for data analyses and data management. All probability values were considered significant at $p < 0.05$.

5. Conclusions

In this large population-based cohort study of adults with treated hypertension, exposure with RH was associated with a significant increased risk of OSA. Overall, this study offers an important step in quantifying the risk of OSA in patients with RH. Importantly, the findings of this study suggests that screening of OSA is necessary in patients with RH. Greater efforts are needed to develop strategies to facilitate screening, monitoring and treatment of OSA.

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