Pulmonary hypertension is associated with an increased incidence of NAFLD: A retrospective cohort study of 18,910 patients

Running title: NAFLD incidence in pulmonary hypertension

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Abstract

Background: Pulmonary hypertension (PH) represents a multicausal disease with increasing global incidence that eventually leads to right ventricular failure. In addition to cardiac sequelae, non-cardiac comorbidities appear to be of increasing relevance, especially in times of improved therapeutic options that often result in long-term survival. Here, we examined a potential association between PH and non-alcoholic fatty liver disease (NAFLD) as well as liver cirrhosis in an outpatient cohort in Germany.

Methods: A total of 9,455 PH patients followed in general and internist practices between 2005 and 2019 were matched by propensity scoring based on age, sex, yearly consultation frequency and relevant co-morbidities (obesity, diabetes, heart failure, lipid metabolism disorders) to a cohort of equal size without PH. The association between PH and NAFLD/liver cirrhosis was evaluated using Cox regression models.

Results: Within 10 years from the index date, cumulative incidence rates of NAFLD were significantly higher among patients with PH (7.3%) compared to non-PH patients (3.5%, log-rank p<0.001). In regression analysis, this association was significant for both female (HR: 1.93, p<0.001) and male (HR: 1.51, p=0.005) patients and was most prominent among patients > 80 years (HR: 3.30, p=0.001). Moreover, PH patients showed a strong trend towards higher incidence rates of liver cirrhosis compared to non-PH patients (1.4 vs. 1.1%, p=0.066).

Conclusion: Our data suggests that incidence rates of NAFLD are strongly elevated in patients with PH. This finding should trigger awareness of non-cardiac comorbidities in these patients and argues for potential liver-directed screening programs in patients with PH.

Introduction

Pulmonary hypertension (PH) describes a chronic elevation of resting mean pulmonary arterial pressure (PAPm) above 20mmHg. Worldwide, it affects about 1% of the population, and up to 10% in the age group over 65 years [1]. The heterogeneous disease is classified into five subgroups based on the underlying etiology using the Nice Classification: 1) Pulmonary Arterial Hypertension (PAH), 2) PH from left heart disease, 3) PH due to pulmonary disease and/or hypoxia, 4) PH due to chronic thromboembolism (CTEPH), 5) PH with unclear multifactorial mechanisms [2]. Life expectancy of patients with PH is limited but has improved in recent decades due to new drug treatment options [3]. Due to the increased pulmonary vascular resistance, adaptive mechanisms result in increasing remodeling of the right ventricle to a high-pressure pump and eventually dilatation of the right ventricle [4]. This leads to increasing right ventricular pump failure with cervical venous congestion, edema, and ascites may occur [5].

Close associations of cardiac and hepatic diseases are well established as many systemic diseases or risk factors affect and damage both organs. In addition, it is known that cardiac diseases, especially chronic heart failure, are risk factors for the development of chronic liver injury, and that cardiac

and pulmonary symptoms can also occur as a result of liver cirrhosis. Right ventricular failure in particular is a known cause for the development of cardiac liver fibrosis and eventually liver cirrhosis [6-8]. On the other hand, portal hypertension has been identified as a risk factor for the development of PH [9]. Further known risk factors for PH include obesity in addition to individual medications, genetic factors, and congenital heart disease [2, 10]. Moreover, it has already been shown that the presence of a metabolic syndrome worsens PH [11]. Non-alcoholic fatty liver disease is a condition that has been on the rise in recent years, particularly in the Western world, and is one of the main causes of liver cirrhosis and hepatocellular carcinoma [12, 13].

However, it has remained largely unclear whether there is an association between PH and the development of NAFLD. We therefore investigated a possible association of these two diseases in a cohort of 9,455 PH-patients matched with a cohort of equal size without PH using the Disease Analyzer database (IQVIA). The aim of our study was to find out whether PH promotes the development of NAFLD and its complications, especially liver cirrhosis.

Materials and methods

Database

This study was based on data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in general and specialized practices in Germany [14]. The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to International Classification of Diseases, 10th revision [ICD-10]), prescriptions (according to Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are constantly being monitored by IQVIA. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialized practices in Germany [14]. The database has been used in previous studies focusing on cardiovascular disorders as well as liver disorders [15, 16].

Ethics approval

The "Disease Analyzer" database, used for analysis, contains anonymized electronic patient records. Patient data was analyzed in aggregated form without individual data being available. An individual consent form was not obtained following national and European legislation.

Study population

This retrospective cohort study included adult patients (≥18 years) with an initial diagnosis of pulmonary hypertension (ICD-10: I27+ original diagnosis text) in 1,274 general and internist practices in Germany between January 2005 and December 2019 (index date; Figure 1). Further inclusion criterium was an observation time of at least 12 months prior to the index date. Patients with a diagnosed liver disease (ICD-10: K70-K77, B18) prior to index date were excluded from the study. After applying the inclusion criteria, patients with PH were matched (1:1) to patients without PH based on propensity scores using a greedy algorithm and derived from the logistic regression using sex, age, yearly consultation frequency, and co-diagnoses (obesity, diabetes, heart failure, lipid metabolism disorders). Diabetes and obesity were used as they are associated with NAFLD. Heart failure and lipid metabolism disorders were used due to the strong correlation with PH. As PH patients have a much higher consultation frequency by GPs due to PH treatment, and higher consultation frequency can increase the probability of other diagnoses documentation, we included consultation frequency per year in the matching. For the non-PH individuals, the index date was that of a randomly selected visit between January 2005 and December 2019 (Figure 1).

Study outcomes and covariates

The main outcome of the study was the incidence of NAFLD (ICD 10: K75.8, K76.0) and liver cirrhosis (K70.3, K74.3-K74.6) as a function of PH.

Statistical analyses

Differences in the sample characteristics between patients with or without PH were tested using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. Cox regression models were conducted to study the association between PH and NAFLD/liver cirrhosis incidence. These models were performed separately for NAFLD and liver cirrhosis. To counteract the problem of multiple comparisons, p-values <0.01 were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS institute, Cary, USA).

Results

Basic characteristics of the study sample

The present study included 9,455 patients with PH and 9,455 patients without PH. Basic characteristics of the study cohorts are shown in Table 1. The mean age [SD] was 72 years [14]. 56.7% of patients were female and 43.3% were male. The average number of GP patients visit was 5.1 (SD: 5.2) times per year during follow-up. Among patients with PH, 33.9% were diabetics, 15.8% were obese, 42.5% had a diagnosed lipid metabolism disorder and 42.2% had a diagnosis of heart failure. Importantly, there were no significant differences between PH and non-PH patients in terms of co-morbidities (Table 1).

Association of pulmonary hypertension and incidence of NAFLD

Within 10 years from the index date, 7.3% of patients with PH but only 3.5% of non-PH patients were diagnosed with NAFLD (log-rank p<0.001, Figure 2). In regression analyses, PH was significantly associated with the incidence of NAFLD (HR: 1.71, 95%CI: 1.39-2.09, p<0.001, Table 2). This association was significant for both female and male patients but more pronounced in women (HR: 1.93, 95%CI: 1.44-2.59, p<0.001) than in men (HR: 1.51, 95%CI: 1.13-2.02, p=0.005). In age-stratified analyses, the strongest association was observed in patients aged >80 years (HR=3.30, 95%CI: 1.60-6.79, p=0.001, Table 2).

Association of pulmonary hypertension and incidence of liver cirrhosis

Within 10 years from the index date, 1.4% of patients with PH and 1.1% of non-PH patients were diagnosed with liver cirrhosis (log-rank p=0.061, Figure 3). In line, regression analyses revealed an increased HR of 1.43 (95%CI: 0.98-2.08) for the development of liver cirrhosis in PH patients, however statistical significance was not reached (p=0.066, Table 3). In sex- and age-stratified analyses, no significant association was observed between PH and liver cirrhosis, most likely due to the small number of patients diagnosed with liver cirrhosis during follow-up (Table 3).

Discussion

In this retrospective cohort study, there was a significant association between PH and NAFLD documented within 10 years after first diagnosis of PH, especially in women and patients older than 80 years. The association between PH and liver cirrhosis was not significant, however there was a clear tendency.

The incidence of NAFLD has increased sharply in recent years and may replace chronic viral hepatitis as the major cause of development of hepatocellular carcinoma in the next few years [17]. However, the development of cirrhosis is not a prerequisite for HCC development in NAFLD; several studies in recent years have shown that up to 42% of NAFLD-associated HCC occur in non-cirrhotic livers [18]. In particular, in the presence of pre-existing liver fibrosis, male gender, age over 60 years, diabetes mellitus, transaminase elevation, and specific genetic risk factors such as PNPLA3, the risk for HCC development is particularly high [19-22]. PH adds as new risk factor for the development of NAFLD and its complications. Our data on the particular association of PH and NAFLD in older patients adds an additional dimension to the problem, since those patients are more prone to side effects of treatments and often display more complicative disease courses. As an example, in case of HCC development, surgical treatment options (including liver transplantation) might be limited in older and comorbid patients.

The development of chronic liver injury secondary to right cardiac decompensation in particular is well known [6, 8]. Interestingly, however, this seems to be independent from the additional NAFLD

development in patients with PH. In both groups we studied, the proportion of patients with heart failure was equal at 42.2%, chronic backflow of blood and hepatic venous congestion cannot be the sole cause of NAFLD development. Classical risk factors such as diabetes and obesity were also similarly prevalent in both studied groups, so that these, too, cannot be causative for the increased NAFLD prevalence in the group of patients with PH. This observation should be the basis for further prospective studies on the development of NAFLD in patients with PH, but also to uncover the possible molecular basis of this disease association. Overall, based on our data, it should be discussed whether the development of hepatic complications should not be regularly monitored after the diagnosis of PH, at least in the subgroup of patients with additional risk factors such as diabetes or obesity, which could subsequently also promote HCC development.

It should be noted, however, that our study has limitations due to its design, which are unavoidable due to the database analysis. On the one hand, misclassifications or missing coding of diagnoses within the ICD-10 coding system cannot be excluded. Furthermore, the German Disease Analyzer Database does not contain laboratory analyses, information on lifestyle or socioeconomic status of the patients, as well as data from hospitals and mortality information. However, the database provides a good overview of GP consultations in Germany and the identification of PH as an independent risk factor for the development of NAFLD is an important step for the initiation of further studies on this issue.

Conclusion

Our data suggests that PH is associated with an increased risk for the development of NAFLD. This finding should trigger awareness of non-cardiac comorbidities in these patients and argues for potential liver-directed screening in patients with PH.

Competing interests

The authors declare no competing interest regarding this publication. KK is employee of IQVIA.

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Tables

Table 1. Basic characteristics of the study sample (after 1:1 propensity score matching)

Variable	Patients with pulmonary hypertension N=9,455	Patients without pulmonary hypertension N=9,455	p-value
Age (years, mean, SD)	72.3 (13.5)	72.3 (13.5)	0.898
Age <=60	16.6	16.7	
Age 61-70	17.8	17.9	0.982
Age 71-80	35.8	35.9	
Age >80	29.8	29.5	
Women	56.7	56.7	1.000
Men	43.3	43.3	
Yearly consultation frequency (total number, mean, SD)	5.1 (5.2)	5.1 (5.2)	1.000
Diabetes	33.9	32.7	0.070
Obesity	15.8	15.7	0.795
Lipid metabolism disorders	42.5	42.8	0.651
Heart failure	42.2	42.2	1.000

Proportions of patients in % given, unless otherwise indicated. SD: standard deviation.

Table 2. Association between pulmonary hypertension and the incidence of NAFLD in patients followed in general and internist practices in Germany (Cox regression models) by age and sex

Cohort	Cumulative 10-year-incidence in patients with pulmonary hypertension (%)	Cumulative 10-year-incidence in patients without pulmonary hypertension (%)	Hazard Ratio (95% CI)	p-value
Total	7.3	3.5	1.71 (1.39-2.09)	<0.001
Age ≤ 60	9.0	3.7	1.82 (1.18-2.81)	0.007
Age 61-70	9.8	5.0	1.57 (1.08-2.28)	0.019
Age 71-80	6.3	3.8	1.54 (1.11-2.15)	0.011
Age > 80	2.8	0.5	3.30 (1.60-6.79)	0.001
Women	5.9	2.8	1.93 (1.44-2.59)	<0.001
Men	9.4	4.5	1.51 (1.13-2.02)	0.005

Table 3. Association between pulmonary hypertension and the incidence of liver cirrhosis in patients followed in general and internist practices in Germany (Cox regression models) by age and sex

Cohort	Cumulative 10-year-incidence in patients with pulmonary hypertension (%)	Cumulative 10-year-incidence in patients without pulmonary hypertension (%)	Hazard Ratio (95% CI)	p-value
Total	1.4	1.1	1.43 (0.98-2.08)	0.066
Age ≤ 60	1.5	1.8	1.18 (0.55-2.53)	0.678
Age 61-70	2.2	0.9	1.60 (0.75-3.40)	0.222
Age 71-80	1.3	0.7	1.70 (0.90-3.22)	0.101
Age > 80	0.5	0.4	0.70 (0.24-2.03)	0.515
Women	1.3	0.9	1.46 (0.82-2.58)	0.197
Men	1.7	1.2	1.41 (0.85-2.34)	0.181

Figure 1.

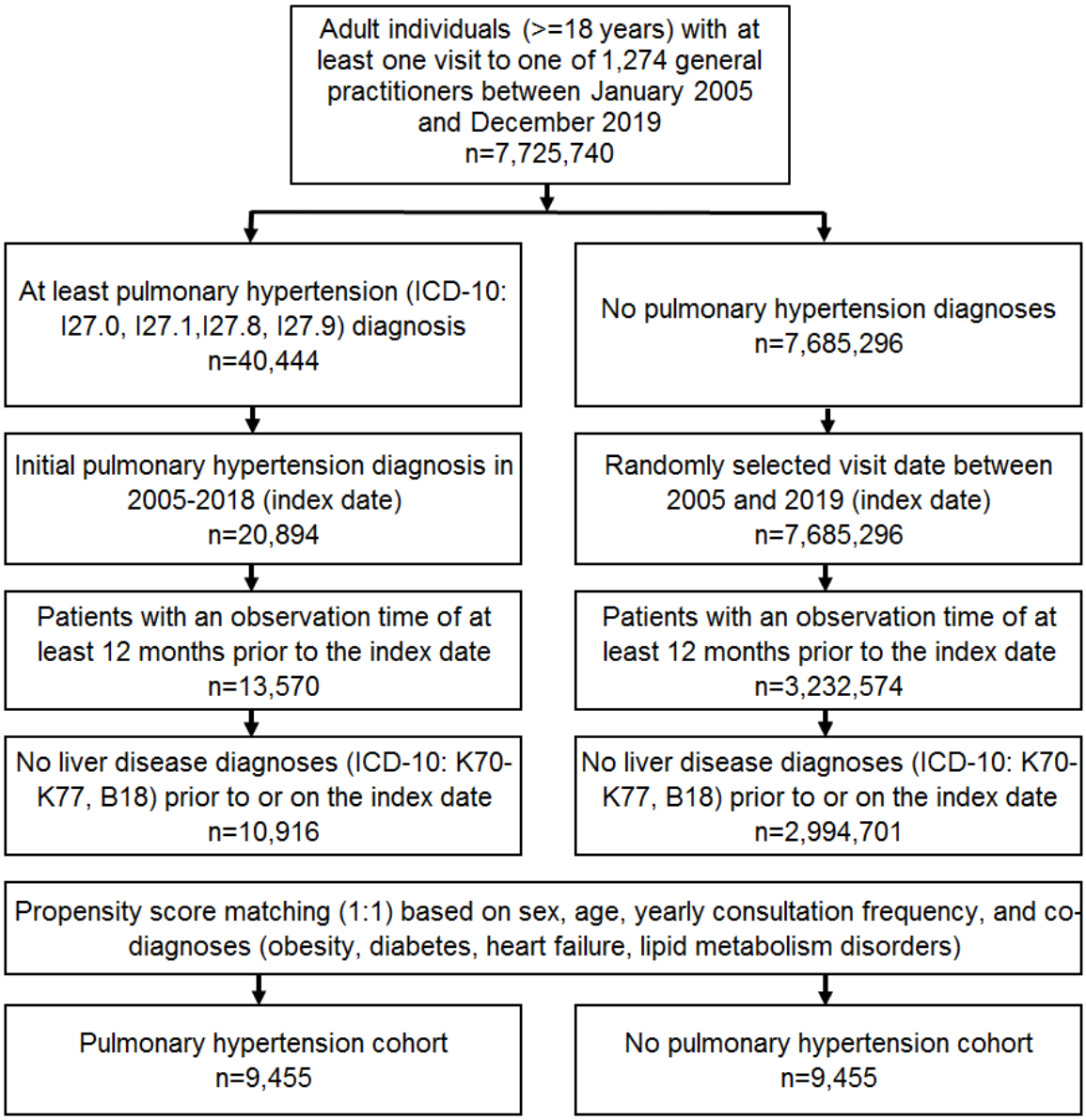

Figure 1. Selection of study patients

Figure 2.

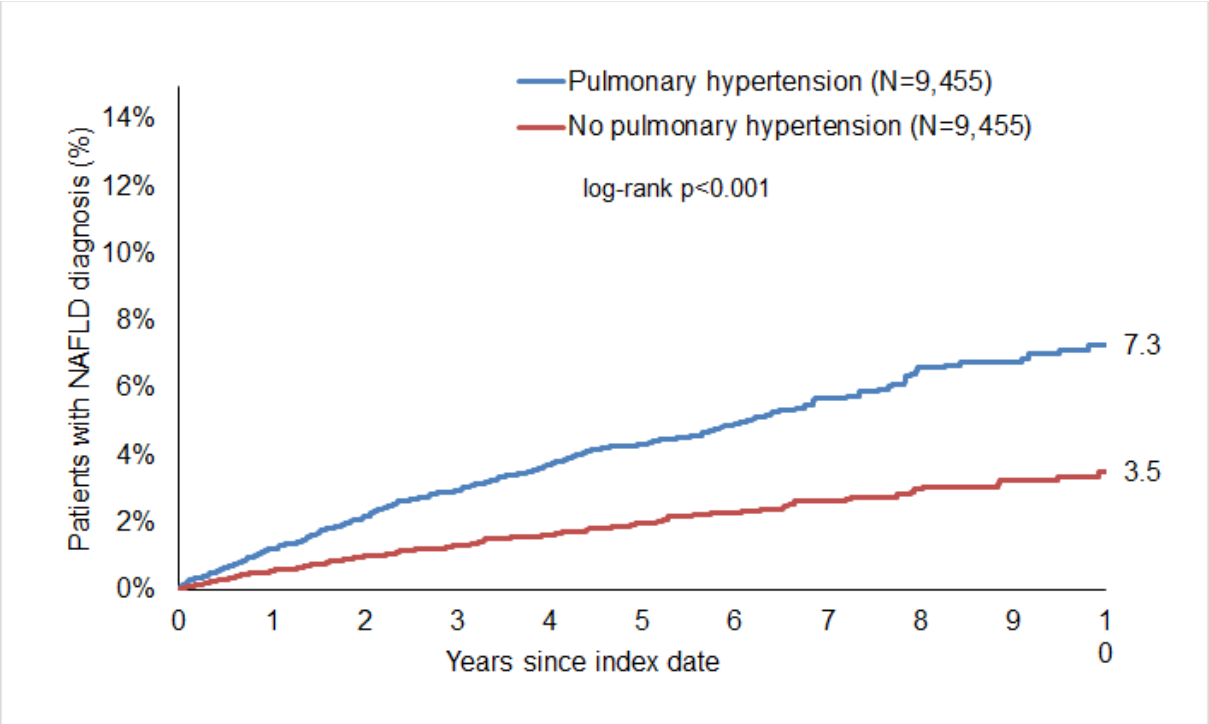

Figure 2. Kaplan-Meier curves for time to NAFLD diagnosis in patients with and without pulmonary hypertension

Figure 3.

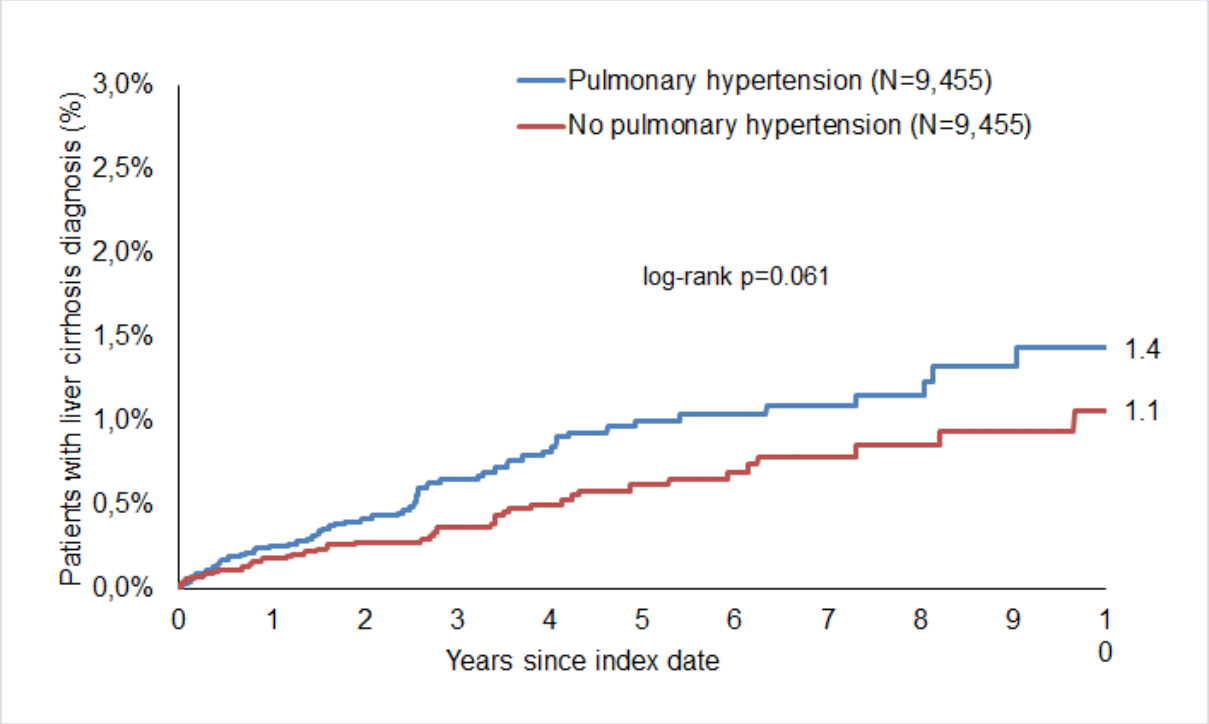

Figure 3. Kaplan-Meier curves for time to liver cirrhosis diagnosis in patients with and without pulmonary hypertension