Economic burden prior to COPD diagnosis: A matched case-control study in the United States

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Summary
Background: In the United States, chronic obstructive pulmonary disease (COPD) diagnosis is often a lengthy process, and consequently results in delays in treatment in early stages. Disease progression and complication may result in increased levels of healthcare service use. To understand the economic burden of COPD prior to diagnosis in the U.S., trends in utilization and costs during the period before initial COPD diagnosis were compared with matched controls.

Methods: A retrospective case-control study was conducted using medical and pharmacy claims data from a large managed care health plan representing a base population of over 30 million covered lives in the U.S. COPD patients with at least 12 months of continuous enrollment and aged 40 years or older were identified (n = 28,968) and matched to up to three random controls (n = 81,322) by age, gender, region of plans and index date. Multivariate regression models were used to estimate average incremental service use and cost between COPD patients and controls. Moreover, trends in utilization and costs for the COPD patients were examined over 36 months before diagnosis.

Results: COPD patients used 1.5–1.6 times more inpatient/emergency department (IP/ED) services and office visits compared to control patients. The average incremental annual costs for IP/ED services, office visits, and medical and pharmacy services were estimated at $550, $238, $1438 and $401, respectively, after adjusting for age, gender, region and comorbid conditions. The 36-month trend analysis showed that COPD patients’ healthcare utilization and costs increased gradually over time, often with a marked increase in the month before COPD diagnosis.
Introduction

Chronic obstructive pulmonary disorder (COPD) is a treatable and preventable lung disease, with a pulmonary component characterized by airflow limitation that is not fully reversible.1 Its burden upon patients, providers, and society is enormous and growing annually. COPD affects more than 20 million Americans2 and is now the fourth most common cause of death (exceeded only by heart disease, cancer and stroke).3 The estimated direct cost of COPD in the United States in 2004 was $20.9 billion. When the indirect cost of COPD due to lost productivity is included ($16.3 billion), the total societal cost of COPD is an estimated $37.2 billion.4 While these numbers represent a significant burden, they are also an underestimate of the true impact of COPD: airflow obstruction contributes to other serious conditions, such as ischemic heart disease, stroke, pneumonia, and lung cancer.5–8

Underdiagnosis of COPD is a serious problem in its management.9–11 There may be as many patients with undiagnosed COPD as those who have been diagnosed.12 In the United States in 2000, approximately 10 million adults responding to the National Health Interview Survey had been diagnosed with COPD, yet 24 million adults with mild or moderate obstructive lung disease (evidence of airflow obstruction identified with spirometric testing) were identified in the National Health and Nutrition Examination Survey (III).4 Other studies have shown that 7.7% of the undiagnosed general population meet the criteria for mild to moderate COPD or asthma.12 Population studies using spirometric assessment of smokers have found a high proportion of undiagnosed COPD or impaired lung function that could progress to COPD.13

Underdiagnosis of COPD is partly due to patient behavior. Many patients fail to recognize the early symptoms of COPD, attributing symptoms instead to aging or smoking itself.14 Others restrict their activities in order to avoid sensations of dyspnea, while underestimating the impact of these symptoms on their daily lives.15 One survey found that roughly three-quarters of early stage COPD patients were either unaware of their condition or reluctant to consult their physician for respiratory symptoms.16 Even patients newly diagnosed with mild to moderate COPD can be reluctant to seek further care from a pulmonologist.17

Late diagnosis of COPD is also partly attributable to providers. Physicians can be reluctant to use the diagnostic term COPD, diagnosing patients instead with asthma, chronic bronchitis, or acute respiratory infection, without examining the underlying disease.18–20 Delays in diagnosis may result in quicker progression of COPD and in inefficient or inappropriate consumption of healthcare services. By the time a diagnosis is made, patients usually have lost half or more of the original lung capacity.21 If COPD could be identified in its early stages, interventions, such as smoking cessation, vaccinations, and other therapies to reduce patients symptoms, could be applied to alter the course and prognosis of the disease, improving the patients’ quality of life.22 Moreover, healthcare utilization and expenditures could be directed toward appropriate treatment sooner. Therefore, the aims of the present study were to estimate the economic burden of undiagnosed COPD in the U.S. by comparing healthcare utilization and costs between a cohort of newly diagnosed COPD patients and a sample of matched controls in the 12 months prior to their initial COPD diagnoses, and to determine trends in utilization and costs over 36 months prior to the COPD diagnosis.

Methods and materials

Study design and data source

This was a retrospective analysis using eligibility, medical, and pharmacy claims data from United Healthcare, a large managed care health plan in the U.S. responsible for coordination of payments for healthcare services. United Healthcare provides health insurance coverage for over 30 million Americans and represents one of the largest health insurance organizations in the U.S. with a variety of plans with varying levels of service coverage. All plans used in the analysis provide fully-insured coverage for physician, hospital and prescription drug services. This database has been used in several epidemiologic and economic studies.23–27 All data are de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Cohort selection

COPD and control cohorts were selected using medical claims data from services provided between January 1, 2003 and June 30, 2004 (the identification period). All subjects had at least 12 months of continuous enrollment in a U.S. commercial health plan with pharmacy coverage and were aged 40 or older in order to ensure benefit entitlement and reduce misclassification bias due to inaccurate claim submissions.

COPD cohort members were identified with: (1) an inpatient hospital (IP) or emergency department (ED) billing claim with a primary diagnosis indicating COPD (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 491.xx, 492.xx, 496.xx); or (2) a physician claim with a primary diagnosis of COPD plus a second medical claim with a COPD diagnosis in any position on a separate service date; or (3) a physician claim with a primary diagnosis of COPD and a pharmacy claim with a primary diagnosis of COPD and a pharmacy

Conclusions: COPD patients in the U.S. consumed substantial healthcare services and costs prior to diagnosis. More timely diagnosis and subsequent treatment may avoid costly healthcare utilization and unnecessary mortality and morbidity post-diagnosis.

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claim for fluticasone propionate/salmeterol combination, salmeterol, ipratropium or tiotropium. Each COPD subject was assigned an index date, the date of the earliest medical claim with a COPD diagnosis during the identification period. COPD subjects were excluded if they had any COPD diagnosis in the 12 months prior to their index dates.

The control cohort was selected from the subset of the general health plan population that had at least one medical claim during the identification period. Each control subject was assigned an index date based on a randomly chosen claim. Control cohort subjects could not have any claims with a COPD diagnosis during the identification period or the 12 months preceding their index date. Thus, the control cohort represented a random selection of conditions to which pre-COPD diagnosis utilization and costs were compared.

Control cohort subjects were matched to COPD subjects up to a 3:1 ratio using the following factors: age range (40–44; 45–54; 55–64; 65–74; 75–84; and 85+), gender, region of plan membership (south, northeast, midwest, west), and month/year of index date. Nearly 96% of COPD subjects had three matches from the control cohort.

Measures

Demographic measures were geographic region, gender, and age. Comorbid conditions were identified from the diagnoses on claims and were grouped using the Clinical Classifications Software developed by Elixhauser and maintained by the Agency for Healthcare Research and Quality (AHRQ). The 20 most prevalent conditions in the study cohorts were identified.

Healthcare utilization and costs were categorized as inpatient hospital (IP), emergency department (ED) visits, office visits, total medical costs and total pharmacy costs. IP and ED, both relatively infrequent, were combined into one utilization variable (IP/ED). Costs were defined as the amount paid by the health plan and the patient, and do not include costs paid by other sources. All-cause healthcare utilization and costs were calculated for each of the 6 months, 7–12 months, 13–18 months, 19–24 months, 25–30 months, and 31–36 months prior to the index date for COPD subjects with at least 36 months of continuous enrollment.

Analysis

Incremental utilization and costs related to COPD diagnosis

Healthcare utilization and cost data for the 12 months prior to the index date were analyzed with multivariate models. Only COPD subjects with three control matches were included in the analyses. The numbers of IP/ED and office visits were modeled using negative binomial (NB) regression. Costs were modeled using Blough et al.’s formulation of a two-part cost model to address skewness of cost data and the large number of $0 costs: a logistic regression was first estimated to examine the determinants, and predict the probability, of any healthcare expenditures during the 12-month pre-index period; costs for subjects with positive (>50) healthcare expenditures were then modeled using a generalized linear model (GLM) with a gamma distribution and log link to account for the skewed distribution of costs. This two-part model avoids potential difficulties introduced by transforming (for example, calculating the log of the costs) and retransforming the dependent variable. In the NB regression, coefficients were presented as incidence rate ratios (IRRs). In the GLM regression, coefficients were exponentiated to represent the ratio of expected costs in the COPD and control cohorts. Predicted costs were also estimated using the GLM coefficients for both cohorts.

Longitudinal trends in utilization and costs

Trends in healthcare utilization and costs over 36 months were analyzed descriptively. Means, standard deviations, and median IP/ED events, office visits, medical costs and pharmacy costs were summarized for each month during the first 6 months and for 6-month intervals 7–36 months preceding the index date. The proportions of the COPD cohorts with positive values in the number of events and costs were also calculated. All tests of statistical significance employed two-tailed tests with an alpha level of 0.05. All analyses were conducted using STATA statistical software, version 8.2 (StataCorp LP, College Station, TX).

Results

Study subjects

Initially 80,914 subjects with COPD diagnosis were identified: of those, 28,968 COPD subjects remained after applying the inclusion and exclusion criteria (Fig. 1). Due to matching, 81,322 control subjects were selected, for an average of 2.8 matches per COPD subject. Of the remaining 110,290 subjects, 100,452 subjects (including 25,113 COPD

Subject identified with COPD: 80,914

At least 40 years of age in 2003: 74,763

No diagnosis of COPD in 12 months prior to index date: 53,321

At least 12 months continuous enrollments: 28,968

Matched control: 81,322

Cohorts with 3 matched pairs
COPD: 25,113
Control: 75,339

Multivariable model analysis

Cohorts with ≥36months continuous enrollment
COPD: 8,697

Trend analysis

Figure 1 COPD and control sample selection. *Note: cohorts for multivariate model analysis had 12 months continuous eligibility and three matched controls. Cohorts for trend analysis had 36 months continuous eligibility.
subjects with three control matches and 75,339 control subjects; 9838 subjects were removed due to incomplete data) were included for multivariable model analysis. The longitudinal trend analysis included 8697 COPD subjects (of the 28,968 COPD subjects) who had at least 36 months continuous eligibility.

**Subject demographics and comorbid conditions**

The distribution of age category, gender and region is presented in Table 1. The 20 most prevalent comorbid conditions by cohorts are shown in Table 2. After the matching, the COPD and control cohorts were of similar age (mean 57.8 years, median 57 years), gender (50.8% male), and geographic mix. The COPD cohort had higher prevalence rates for a variety of comorbid conditions compared with the control cohort. As expected, two of the three most prevalent conditions in the COPD cohort were respiratory-related (i.e., respiratory infections and other lower respiratory disease). Hypertension, heart disease, and lipid disorders were among the prevalent conditions in both cohorts, however more prevalent in the COPD cohort (43% vs. 15% for hypertension, 41% vs. 9% for disease of the heart, and 37% vs. 15% for lipid disorders, respectively).

**Incremental utilization and costs in 12 months**

The results of negative binomial regressions to model the numbers of IP/ED visits and office visits during the 12-month pre-index date period are displayed in Table 3. The COPD cohort used significantly more resources than the control cohort. The point estimate for the IRR indicates that COPD patients had 1.6 times more IP/ED visits and 1.5 times more office visits compared with non-COPD patients after adjusting for age, gender, region, and the most common comorbid conditions.

The results of the two-part models of IP/ED costs, office visit costs, medical costs and pharmacy costs are summarized in Table 4. The logistic regressions show that COPD diagnosis was associated with significantly greater odds of incurring positive costs (i.e., any costs; 1.6 times for IP/ED services, 1.9 times for office visits, 3.3 times for medical services and 1.4 times for pharmacy services) compared with the control cohort. The GLM results show that, among patients with positive costs, the COPD cohort had significantly higher IP/ED, office visits, medical and pharmacy costs relative to the controls. COPD diagnosis was associated with 1.3–1.6 times higher costs after adjusting for background characteristics. The average estimated costs in the COPD and control cohorts were $1229 and $679 for IP/ED services, $646 and $408 for office visits, $3367 and $1929 for medical services, and $1242 and $841 for pharmacy services, respectively, during the 12-month pre-index date period.

**Longitudinal trends in utilization and costs over 36 months**

The trends in all-cause IP/ED visits and office visits utilization for the COPD cohort are graphically presented in Fig. 2. The trends of all-cause medical and pharmacy costs are presented in Fig. 3. Mean, standard deviation (SD) and median numbers of IP/ED visits, office visits, total medical costs and total pharmacy costs are summarized in Table 5. Within the COPD cohort, resource use and costs showed a slight upward trend toward the COPD diagnosis. The number of office visits and pharmacy costs appeared to increase relatively steadily over time. However, dramatic increases were observed in the IP/ED visits and medical costs during the month immediately preceding COPD diagnosis.
Discussion

Summary of findings

The retrospective administrative claims analysis revealed that COPD patients in the U.S. had significantly more healthcare utilization and higher costs across all services examined in the year prior to COPD diagnosis than matched control subjects. The COPD patients, on average, had 1.5 to 1.6 times more IP/ED visits and office visits, and incremental annual costs for IP/ED visits, office visits, and medical and pharmacy services were estimated as $550, $238, $1438 and $401, respectively, after adjusting for age, gender, region of the U.S. and comorbid conditions. The trend analysis for COPD patients showed that healthcare utilization and costs slightly increased over time and were most frequently consumed in the month before COPD diagnosis.

The differences in healthcare utilization and costs between the COPD and control cohorts may be explained by baseline health conditions. The COPD patients had significantly higher prevalence rates of respiratory and non-respiratory comorbid conditions, such as hypertension and heart disease, which may be attributed to a common causal agent, tobacco smoking. However, even after adjusting for these characteristics, the COPD diagnosis was associated with significantly higher resource utilization and treatment costs.

The findings from this study provide information to assess disease progression and treatment patterns among the COPD patients prior to diagnosis. The gradual increases in healthcare contact might be reflected by the gradual worsening of health conditions over time, even before the COPD diagnosis. Sudden increases in IP/ED visits might indicate that COPD was not diagnosed until patients experienced an acute exacerbation, or sudden worsening of respiratory conditions. Some portion of the services and costs might have been avoided by earlier diagnosis and

<table>
<thead>
<tr>
<th>Comorbid condition</th>
<th>COPD cohort</th>
<th>Control cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank</td>
<td>n (%)</td>
<td>Rank</td>
</tr>
<tr>
<td>Factors influencing healthcare</td>
<td>1 14,970 (51.7)</td>
<td>1 18,220 (22.4)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>2 12,831 (44.3)</td>
<td>10 6532 (8.0)</td>
</tr>
<tr>
<td>Other lower respiratory disease</td>
<td>3 12,530 (43.3)</td>
<td>20 3408 (4.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 12,337 (42.6)</td>
<td>2 11,958 (14.7)</td>
</tr>
<tr>
<td>Diseases of the heart</td>
<td>5 11,904 (41.1)</td>
<td>7 7431 (9.1)</td>
</tr>
<tr>
<td>Symptoms, signs, ill-defined conditions</td>
<td>6 11,477 (39.6)</td>
<td>6 8083 (9.9)</td>
</tr>
<tr>
<td>Disorders of lipid metabolism</td>
<td>7 10,797 (37.3)</td>
<td>3 11,830 (14.6)</td>
</tr>
<tr>
<td>Residual codes, unclassified</td>
<td>8 8705 (30.1)</td>
<td>8 7192 (8.8)</td>
</tr>
<tr>
<td>Other connective tissue disease</td>
<td>9 8516 (29.4)</td>
<td>11 6179 (7.6)</td>
</tr>
<tr>
<td>Non-traumatic joint disorders</td>
<td>10 8423 (29.1)</td>
<td>9 6718 (8.3)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>11 7966 (27.5)</td>
<td>5 8822 (10.9)</td>
</tr>
<tr>
<td>Spondylosis, intervertebral disc, other back problems</td>
<td>12 7435 (25.7)</td>
<td>13 5323 (6.6)</td>
</tr>
<tr>
<td>Diseases of female genital organs</td>
<td>13 6793 (23.5)</td>
<td>4 9694 (11.9)</td>
</tr>
<tr>
<td>Diseases of the urinary system</td>
<td>14 6388 (22.1)</td>
<td>15 4477 (5.5)</td>
</tr>
<tr>
<td>Other skin disorders</td>
<td>15 5766 (19.9)</td>
<td>12 5806 (7.1)</td>
</tr>
<tr>
<td>Other upper respiratory disease</td>
<td>16 5700 (19.7)</td>
<td>18 3542 (4.4)</td>
</tr>
<tr>
<td>Asthma</td>
<td>17 5695 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Other nervous system disorders</td>
<td>18 5613 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal disorders</td>
<td>19 5417 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Diseases of arteries, arterioles, capillaries</td>
<td>20 5327 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Infections and screening for infectious disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>16 4464 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Ear conditions</td>
<td>17 3615 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus without complications</td>
<td>19 3487 (4.3)</td>
<td></td>
</tr>
</tbody>
</table>

Comorbid conditions were identified from diagnoses on claims and were grouped using the Clinical Classifications Software developed by Elixhauser and maintained by the Agency for Healthcare Research and Quality (AHRQ). Blank table entries indicate conditions which were not ranked among the top 20 most frequently occurring for the specific cohort.

Table 3  Effect of COPD diagnosis on healthcare utilization

<table>
<thead>
<tr>
<th>Outcome measures (number of events per year)</th>
<th>Regression model</th>
<th>IRRs (robust 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP/ED visits</td>
<td>Negative binomial model</td>
<td>1.583 (1.475–1.699)</td>
</tr>
<tr>
<td>Office visits</td>
<td>Negative binomial model</td>
<td>1.544 (1.508–1.581)</td>
</tr>
</tbody>
</table>

Incidence rate ratios (IRRs) were calculated by adjusting for age categories, gender, region of plan membership, asthma diagnosis (ICD-9-CM code 493.xx), and 23 most common comorbidities (excluding asthma) listed in Table 2. IP: inpatient hospital, ED: emergency department.
initiation of treatment. The findings may be reflective of the current evidence in the U.S. that COPD diagnoses often occur in the moderate stage. However, findings differ from a phone interview study conducted in Northern Sweden which found that COPD patients with a diagnosis of COPD ($2207) had higher healthcare and productivity costs than COPD patients without a diagnosis ($1128). Discrepancies in the findings between this study and the OLIN study are most likely due to healthcare utilization and care seeking behavior since the controls in this study were also patients and sought care for other ailments, compared to the OLIN study which was more community based assessment.

### Study limitations

In addition to the common limitations known to administrative claims analysis and observational studies such as missing data on key confounders such as demographics, socioeconomic status, clinical validation, disease severity, etc., there were study-specific limitations that must be considered in interpreting the results. For this study, the AHRQ comorbidity indicators were used to control for baseline differences in the multivariate regression models. However, because of their discrete nature, the indicators did not provide information about relative illness burden or severity of conditions.

Other types of severity measures and risk adjusters, such as Charlson comorbidity index and sums of utilization/costs during a previous period, often are used in claims data analyses because they summarize a patient’s illness burden in a single value. It was important, however, to understand the mechanics of each measure and its inherent limitations. For example, some risk adjusters use only claims from inpatient services or were developed to predict mortality, which may not be sufficient to detect the impact on utilization and costs. Thus, using the AHRQ comorbidity indicators to capture the breadth of conditions that affected this study population was considered as an appropriate choice to meet the study purpose. Even more so important, is the lack of data on COPD severity as defined by GOLD stage. These data, determined through pulmonary function test results, are not available in administrative billing data and were therefore

### Table 4  Effect of COPD diagnosis on healthcare costs

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Logistic regression (any costs) [odds ratio (robust 95% CI)]</th>
<th>GLM model for patients with costs &gt; 0 [exp(coefficient) (robust 95% CI)]</th>
<th>Predicted costs for COPD cohort [annual costs]</th>
<th>Predicted costs for control cohort [annual costs]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP/ED costs</td>
<td>1.635 (1.545–1.730)</td>
<td>1.344 (1.205–1.499)</td>
<td>$1229</td>
<td>$679</td>
</tr>
<tr>
<td>Office visit costs</td>
<td>1.861 (1.685–2.056)</td>
<td>1.493 (1.404–1.587)</td>
<td>$646</td>
<td>$408</td>
</tr>
<tr>
<td>Medical costs</td>
<td>3.284 (2.866–3.764)</td>
<td>1.634 (1.542–1.732)</td>
<td>$3367</td>
<td>$1929</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td>1.417 (1.343–1.496)</td>
<td>1.369 (1.326–1.415)</td>
<td>$1242</td>
<td>$841</td>
</tr>
</tbody>
</table>

Odds ratios and exponentiated coefficient were calculated by adjusting for age categories, gender, region of plan membership, asthma diagnosis (ICD-9-CM code 493.xx), and 23 most common comorbidities (excluding asthma) listed in Table 2. IP: inpatient hospital, ED: emergency department.

### Figure 2  Trend in healthcare utilization over 36 months prior to COPD diagnosis.
not available for assessment in this study. Staging of COPD at diagnosis is very likely to be confounding the assessment of cost, as someone who is diagnosed with more advanced disease is much more likely to have increased costs prior to diagnosis; however the results of this study have provided details of trends in the diagnosis of COPD at a population level in the U.S.

Moreover, there was a concern about simultaneity bias, in which comorbid conditions and the outcome measures, utilization and costs, were measured during the same time period.\textsuperscript{38} It could be assumed that having a comorbid condition would affect the number of visits and costs. At the same time, a patient who had frequent contacts with a physician might be more likely to get a diagnosis. If this simultaneity exists, the estimated effect of COPD diagnosis could be biased. Nevertheless, it would be also true that omitting relevant variables which were positively related to the outcomes could cause upward bias.

The results of this study provide valuable insight regarding the progression of healthcare resource utilization leading up to a COPD diagnosis. The month-by-month examination of utilization and costs in this study revealed a pattern of increasing healthcare resource consumption and expenditures, often with a dramatic increase in the month prior to diagnosis. These ''spikes'' in IP/ED encounters and medical costs may be directly attributable to the actual diagnosis of COPD. That is, they may reflect increasing utilization as these patients’ physicians ruled out...
other diagnoses and focused on a diagnosis of COPD, or they may reflect increasing exacerbations of symptoms that led to a COPD diagnosis.

The consequences of an earlier diagnosis of COPD with appropriate treatment may reduce this unnecessary burden. In the short term, once diagnosed, healthcare utilization and costs would increase because COPD patients are given treatments to control their symptoms. However, in the long term, total treatment costs would be saved because costly outcomes (i.e., inpatients/emergency department visits) are avoided by appropriate treatments. An examination of the utilization and costs following COPD diagnosis would provide a more complete understanding of the progression of care for this condition and impact of diagnosis.

**Conflict of interest statement**

Manabu Akazawa, Rachel Halpern, and Aylin Riedel received financial support from GlaxoSmithKline. Richard Stanford and Anand Dalal are employees of GlaxoSmithKline. Christopher Blanchette was an employee of GlaxoSmithKline during the conduct of this study. Rachael Halpern, Aylin Riedel, and Christopher Blanchette have received financial support from other pharmaceutical manufacturers.

**Acknowledgement**

All authors contributed to the study design, collection, analysis and interpretation of data, writing of the manuscript, and in the decision to submit the manuscript for publication.

**References**


