Burden of Illness and Healthcare Resource Use in US Patients with sporadic Inclusion Body Myositis

Gorana Capkun[1], PhD; Aoife Callan[2], PhD; Haijun Tian[3], PhD; Zhongyuan Wei[4], MS; Changgeng Zhao[3], PhD; Neetu Agashivala[3], MS; Victoria Barghout[5], MSPH

[1] Novartis AG, Basel Switzerland

[2] Novartis Global Service Center Dublin, Ireland

[3] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

[4] KMK Consulting, Inc., Morristown, NJ, USA

[5] VEB HealthCare LLC, Morristown, NJ, USA

Acknowledgements

The authors are grateful to Pelle Stolt for writing assistance and to Jenny Fang and Kristen Johnson for helpful comments on the manuscript and Vijayalakshmi Vasanthaprasad for editorial and submission support.

Abstract word count: 146/150

Manuscript word count: 3409/4000

Corresponding author: Gorana Capkun

Address for correspondence: Novartis AG, Basel Switzerland

Email: gorana.capkun-niggli@novartis.com

Running title: Economic Burden of sIBM patients in the US

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/mus.25686

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Disclosure of Conflicts of Interest: This project was sponsored by Novartis AG. Gorana Capkun, Aoife Callan, Haijun Tian, Changgeng Zhao, and Neetu Agashivala are, or were employees at Novartis at the time of performing the analysis.

Title: Burden of Illness and Healthcare Resource Use in Patients with sporadic Inclusion Body Myositis

Abstract

Introduction: We analyzed the burden of illness of sporadic Inclusion Body Myositis (sIBM) patients and the costs to the healthcare system.

Methods: A retrospective cohort analysis of 333 sIBM patients aged ≥50 years was performed using United States claims data. sIBM patients were matched in a 1:5 ratio to randomly selected individuals with ≥1 healthcare encounter within the year of index date.

Results: sIBM patients presented with higher rates of disease- and muscle-related conditions, such as myalgia, myositis, muscle weakness, dysphagia, pneumonia and falls. Use of healthcare resources, including physical therapy, office visits, ER visits and hospitalizations, was greater in sIBM patients. This was also reflected in significantly higher overall healthcare costs in the sIBM population driven mainly by more all-cause office visits, all-cause ER visits and hospitalizations.

Discussion: sIBM imposes a substantial burden on US patients in terms of additional healthcare utilization and associated costs.

Key words: Inclusion body myositis, Sporadic IBM, Disease burden, Cost, Healthcare resource use, Retrospective cohort study

Introduction

Sporadic inclusion body myositis (sIBM) is a slowly progressive inflammatory myopathy characterized by asymmetric weakness and atrophy of proximal and distal muscles, diminished deep tendon reflexes, difficulty in swallowing, and a variety of pathological changes leading to muscle-fiber degeneration, severe disability and loss of quality of life (QoL). Although it is a rare disease, sIBM is thought to be the most common progressive myopathy presenting in those over 50 years of age.[1,2] There is often a substantial delay, typically around five years, between disease onset and diagnosis, attributable to the rarity of the disease, lack of disease awareness among clinicians as well as patients, and diagnostic difficulties.[3,4]

The prevalence of sIBM varies from 1 to 71 per million, increasing up to 139 per million in people over the age of 50.[4,5] sIBM has a male predominance and usually does not affect individuals below the age of 45.[1] There is currently no therapy with demonstrated efficacy in sIBM. Treatment with anti-inflammatory or immunomodulatory agents have not demonstrated convincing effectiveness on slowing down, stopping or reversing sIBM progression, and are known to cause potentially serious adverse events.[6] Few data from randomized clinical trials are available and because of the rarity of the disease, trials have mostly been small.[6, 7] Without effective pharmacotherapies, management tends to be limited to speech and language therapy for patients with dysphagia, dietary support, and physical and occupational therapy. The progressive and debilitating nature of sIBM indicates that the disease imposes a substantial burden of illness on patients and associated costs to healthcare systems, but the impact of sIBM on healthcare resource use is unknown. The

International Classification of Diseases – Clinical Modification, Ninth Revision (ICD-9 CM) code for sIBM was not generated until 2010, thereby limiting any prior undertaking of database analyses of sIBM patients.[8]

Healthcare in the United States (US) is largely operated by private sector consisting of many distinct organizations systematically tracking the financial transactions between health care providers and patients in forms of administrative claims databases. Real-world evidence collected through administrative claims databases is therefore a rich source of information and particularly helpful in describing burden of diseases. In the present study, we analyzed data from a US administrative claims database to provide a claims-based assessment of the healthcare use and associated costs in patients diagnosed with sIBM patients compared with matched control patients from the general population.

Methods

Study design and patients

A retrospective cohort analysis of US patients using Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database data from January 1, 2009 to December 31, 2013 (identification period) was conducted. Patients were included if they were ≥50 years of age, had ≥2 outpatient diagnoses of sIBM (ICD-9-CM: 359.71) from outpatient claims on different dates ≥7 days apart or ≥1 inpatient diagnosis between January 1, 2010 and December 31, 2012 (study period). The date of the first diagnosis of sIBM during the study period was defined as the index date. Only patients who had continuous healthcare plan enrollment for 12 months before and 12 months after the index date were included. Patients were excluded if they had a diagnosis of congenital hereditary muscular dystrophy (ICD-9-CM: 359.0) or hereditary progressive muscular dystrophy (ICD-9-CM: 359.1) in the identification period.

sIBM patients were matched in 1:5 ratio[9] to randomly selected individuals with at least one healthcare encounter within the year of the sIBM patient's index date (control patients).[10] Patients were matched on index year, age, sex and continuous enrolment in a healthcare plan. Matched control individuals were assigned the same index date as sIBM patients. Patients were excluded from the control population if they had a diagnosis of sIBM or a potentially competing diagnosis: polymyositis, congenital hereditary muscular dystrophy or hereditary progressive muscular dystrophy, chronic inflammatory demyelinating polyneuropathy, chronic inflammatory, symptomatic inflammatory myopathy in diseases classified elsewhere, other myopathies, myopathy unspecified, Sjogren's disease,

dermatomyositis, myotonic disorders, periodic paralysis, toxic myopathy, myopathy in endocrine diseases classified elsewhere, and dementia. For the analysis of healthcare-resource use, baseline was set at 12 months before the index date. Data were analyzed at baseline and at 12 months after the index date. Sensitivity analyses were also performed with relaxed inclusion criteria: relaxing the definition of sIBM patients requiring only one ICD-9-CM code for sIBM or including sIBM patients with a competing diagnosis from analysis.

Data source

The Truven Health MarketScan® Commercial Claims and Encounters and Medicare Supplemental Research databases[11-13] were used for the analysis. The databases combines data from >130 million inpatients and outpatients, linking paid claims and encounter data to detailed patient information across locations and types of providers and over time. These nationally representative databases capture person-specific clinical resource use, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services which are not covered in a health insurance contract. The carve-out services are usually reimbursed according to a different arrangement or rate formula than those services specified under the contract umbrella.

All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996. No identifiable protected health information was extracted during the course of the study. Hence, this study did not require informed consent or institutional review board approval.

Study variables

Demographic data (age, sex, geographic region, healthcare plan and employment status) were collected at index time. Additional data collected during the baseline period (12 months prior to index date) included the Charlson comorbidity index (CCI), a weighted index calculated according to the number of morbidities affecting an individual, taking into account the number and the seriousness of comorbid diseases.[14] The following 18 variables reflect the main objectives of the manuscript: occurrence of physical therapy evaluation, muscle biopsy, electromyography, physical performance test, physical therapy, assisted device usage, walker, wheel chair, power wheel chair, Magnetic Resonance Imaging (MRI), dyspnea, falls, aspiration pneumonia, pneumonia, office visits, emergency-room (ER) visits, hospitalizations 12 months after index date, all cause healthcare costs.

Statistical methods

Descriptive statistics were provided for the above variables. For continuous variables, means and standard deviations are presented, for categorical variables, counts and percentages are presented. Bivariate comparisons of comorbidities and conditions of interest between sIBM and the matched control group were conducted using t-test, chi-square test and non-parametric tests as appropriate. Negative Binomial Generalized Estimating Equation models were used to compare all-cause hospitalizations, all-cause ER visits and all-cause office visits between sIBM patients and matched controls. Generalized linear regression with a log link and Gamma distribution or 2-part models[15] were used to compare and predict health care utilization costs in the follow-up period between sIBM patients and matched controls. The first part of the model used logistic regression to calculate the probability of nonzero costs

and the second part uses a generalized linear regression with a log link and Gamma distribution for the costs, conditional on nonzero costs. All models controlled for the matching structure, as well as age, sex, geographic region, insurance type, sIBM-related conditions at baseline (dysphagia, pneumonia, aspiration pneumonia, and falls), baseline CCI score, baseline medication burden and baseline healthcare utilization. For the cost models, the adjusted mean costs were reported for sIBM patients and matched controls in terms of US dollars and bootstrapping 95% confidence intervals (CIs). All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). Statistical significance of the comparison between sIBM and control patient cohorts for the 18 main variables was considered to be reached if the p-value was <0.0028 according to the one-step Bonferroni method for multiplicity adjustment.

Results

Demographics

333 sIBM patients, with a mean age of 69 ±9.6 years, were identified. The patients were matched to 1,665 patients without sIBM. Demographic characteristics at the index date are shown in Table 1, with the greater prevalence of men (66%); no differences were observed between the two groups for age and sex. Patients were also similar with respect to health plan type. At baseline, patients with sIBM had greater mean CCI score than the control population. In addition, mean medication burden expressed as a mean number of drug classes was also higher in sIBM patients than the control group at baseline.

A breakdown of the ten most common comorbidities and sIBM-related conditions in sIBM patients and a comparison with the control patients at baseline are shown in Figure 1. Except for hypertension, there were no major differences in cardiovascular comorbidities between sIBM patients and the control group ($p=0.0020$). Hypertension was the most common comorbidity in both patient groups and rates of diabetes mellitus and hyperlipidemia were similar in both groups. However, sIBM patients presented with several-fold higher rates of disease and muscle-related conditions such as myalgia and myositis (47% vs. 3% in controls) or muscle weakness (32% vs. 2%). The difference between the groups were significant ($p<0.0001$).

Rates of many sIBM-related conditions at baseline were significantly higher in patients with sIBM than in the control group (Figure 2). Rates of dysphagia were several-fold higher and rates of aspiration pneumonia, while low at baseline, were higher in patients with sIBM.

Rates of falls were high in the sIBM population in the baseline period compared with the control population. Rates of sIBM –related conditions remained higher in patients with sIBM that the control group during the 12 months after index date (Figure 2).

Drug utilization

The average number of medications per patient per year was higher in patients with sIBM during the 12 month before index date (6.9±6.4 vs 5.5±5.2 p-value: 0.0001). Although a substantial percentage of medications in both groups during the 12 months after index date were drugs for cardiovascular disease, sIBM patients took more analgesics and anti-inflammatory drugs (in particular opioid analgesics and acetaminophen or their combinations) and corticosteroids (prednisone) than non-sIBM patients. During the 12 months after index date, sIBM patients also had higher use than non-sIBM patients of intravenous immunoglobulin and immunotherapies, mostly methotrexate (Supplementary table 1).

Healthcare utilization and costs

Patients with sIBM underwent more medical procedures that may be associated with the management of sIBM than the control group (Supplementary table 2). Muscle biopsies were performed only in sIBM patients. A significantly higher proportion of sIBM patients compared to non-sIBM patients received MRIs at baseline and in the 12 months after the index date. Physical therapy evaluation was also considerably higher in sIBM patients during the 12 months after index date. sIBM patients also had ten-fold more frequent assisted device use than the general patient population over the 12 months after index date.

Overall, annual all-cause healthcare resource use was higher among sIBM patients. The differences were driven mainly by more all-cause office visits (11.4 vs. 7.0%, p<0.0001), but sIBM patients also showed significantly higher rates of all-cause ER visits (1.0% vs. 0.4, p<0.0001) and hospitalizations (0.4 vs. 0.1, p<0.0001). Twelve months after index date and adjusting for baseline characteristics, sIBM patients had significantly higher risk of all-cause hospitalization, (incidence rate ratio [IRR]: 1.85; 95% CI: 1.42–2.43), all-cause ER visits (IRR: 1.75; 95% CI: 1.41–2.19) and office visits (IRR: 1.33; 95% CI: 1.23–1.43).

The greater use of healthcare resources in sIBM patients translated into significantly higher (p<0.0001) overall costs for healthcare in this population than in the general population of patients (Table 2). Approximately 14% of overall healthcare costs were due to prescription drugs. The major drivers of cost differences were increased outpatient visits cost and all-cause medical costs. Inpatient costs, ER costs and costs of drugs were also higher in sIBM patients than in the control population. The sensitivity results were similar to those in the main analysis (data not shown).

Discussion

sIBM is known to impose a heavy burden of illness on patients due to disease-associated disability and loss of QoL.[16] The present study quantified this burden by analyzing data on both incident and prevalent patients in a US claims database. These data show that more sIBM patients experienced sIBM-related conditions, underwent more procedures, and received more analgesics and anti-inflammatory drugs than patients without sIBM, matched for age, sex and geographic location. In addition, patients with sIBM had 50% greater annual all-cause healthcare resource uses than non-sIBM patients. The annual all-cause healthcare costs to sIBM patients were more than twice than those incurred in the control group. The greatest drivers of healthcare resources were increased outpatient visit costs and all-cause medical costs. Costs of drugs, although higher in sIBM patients, made only a small contribution to the increased costs overall. This can be partially explained by the absence of sIBM specific treatments.

It appears paradoxical that sIBM, a condition that leads to severe disability and major loss of QoL, has not been widely analyzed for its impact on the use of healthcare resources. The lack of effective, well-tolerated pharmacotherapies is a probable reason, as well as the fact that no ICD 9-CM code for sIBM was available until 2010. The data used in the current analysis, from a large population over a 2-year observation period has not been available previously. In order to study a rare disease using claims database, the ICD-9 or 10 codes should be available for at least 1 or two years for physicians to reliably use the new diagnostic code and to allow for sufficient number of patients for the study.[17] Earlier analyses of US claims databases have included idiopathic inflammatory myopathies as a group, without the ability

to distinguish sIBM from the other myopathies.[18, 19] Retrospective claims database analysis in rare diseases have been usually to collect epidemiological data.[20] Recently, such study designs are being used to understand burden of rare diseases too.[21] The comorbidity profile of sIBM patients looks similar to the profile of idiopathic inflammatory myopathies. Medical costs are mainly driven by office visits. However, sIBM patients seem to have higher medical costs than patients with dermatomyositis, polymyositis and interstitial myositis.

These data are relevant to US payers who are tasked with allocating resources and redesign of private health benefit plans and Medicaid programs to implement cost-savings initiatives. Beyond the US, the current study provides an analysis of burden of illness in sIBM patients and an indication of the importance of this disease and its demands on various aspects of healthcare.

Our findings confirm what has been reported from epidemiological surveys: the sIBM population was similar to sIBM populations described in demographic surveys,[22-24] demonstrating a greater prevalence of sIBM in men and evidence of specific co-morbidities. Although the two matched study populations had similar rates of common cardiovascular disease, muscle-associated conditions were up to ten times more frequent in sIBM patients. It has been reported that after a median time of seven years from disease onset, two-thirds of patients with sIBM will have lost their independent walking ability;[25] the weakness associated with the disease was reflected in high rates of physical therapy, assisted device use and physical rehabilitation in our cohort.

The most common sIBM-related conditions identified in the population were dysphagia and pneumonia. While further research is required to establish if sIBM is directly associated with reduced life expectancy,[22] such disease-related conditions may adversely impact mortality. Survey data indicate that the risk of premature mortality is several-fold higher in sIBM patients than in an age-matched population.[26] Pneumonia has been reported as the cause of death in up to 28% of patients with sIBM.[27] In addition, a number of studies have found aspiration pneumonia to be a common cause of death in sporadic IBM.[27,28,29] Thus, the nearly two-fold greater prevalence of both pneumonia and aspiration pneumonia in patients with sIBM compared to healthy controls within the 24 month analysis period may indicate severe consequences for patients, although such an interpretation would need to be substantiated by outcomes data and is beyond the scope of the current study. Aspiration pneumonia from sIBM-associated dysphagia and the general immobility from the disease are thought to contribute to the severity of pneumonia in sIBM.[28] Another indication of potentially increased mortality risk in the sIBM population is the higher frequency of sIBM patients with a CCI ≥ 3 compared with the control population observed in this analysis. Higher CCI has been shown to be predictive of in-hospital death, overall death and of death from many comorbid diseases.[30,31]

Dysphagia and has been reported to be problematic for 40-50% of sIBM patients.[32] It can lead to frequent choking and malnutrition, and if sufficiently severe may warrant placement of a percutaneous endoscopic gastrostomy (PEG) tube. In the current study, the follow-up period was limited to 12 months, which is too short for a reliable estimate of long-term risk of dysphagia. In consequence, the rates of dysphagia observed in the current study

population were lower than those reported from long-term data in the literature. Our analysis did not allow for a comparison of changes in rates over time, but the rates of dysphagia and pneumonia 12 months after the index date were numerically greater than those at baseline, which would be consistent with the progressive nature of sIBM. It can reasonably be assumed that patients' clinical status, and consequently the disease-associated healthcare use and costs, will increase further with time in the study population. No such differences between baseline and 12 months after the index date were found for the rates of falls, but this result needs to be viewed against the nature of the database used. In general, sIBM patients are at risk of falls and thus restrict mobility or change their walking behavior. They often undergo falls management to reduce further falls events.[1, 16] In a claims database, falls would be recorded only if they lead to healthcare resource utilization. When surveyed with a questionnaire, >60% of people with sIBM typically report a history of falls, but only a fraction of patients report seeking care for falls or receiving falls management input.[33] Hence, it is likely that the rates of falls were underreported in our population. Targeted surveys would be needed to capture the range of falls and their impact on patients.

The analysis focused on assessing and quantifying healthcare resource use. The impact of sIBM on patient-related outcomes such as daily activities or QoL could not be analyzed from the claims database. Indeed, there are few studies on this subject available, although work to develop and validate a patient-reported measure of physical functioning in sIBM, the sporadic Inclusion Body Myositis Physical Functioning Assessment (sIFA), was recently completed.[34,35] There are reports of significant reductions in the physical functioning, role physical, general health and social functioning domains of the Short Form (SF)-36

instrument, but little work has been done on the impact of psychosocial factors such as mood on QoL.[36] Thus, even the substantial disease-associated healthcare utilization in sIBM patients demonstrated in the current dataset may be an underestimate, as it does not include QoL-associated costs to patients, society and informal caregivers. Use of walkers, wheelchairs, and other assistive devices are also likely to be under-represented as these can be purchased in retail outlets and paid for out of pocket.

The strength of this observational, retrospective analysis is the use of a claims database, with sIBM diagnoses and those of comorbidities made according to standardized ICD 9-CM codes. The inclusion of 333 sIBM patients is also respectable, given the rarity of the condition. Nevertheless, the analysis has a number of limitations that need to be acknowledged. The selection of sIBM patients depend on the accuracy of the diagnosis and the correct assignment of the ICD 9-CM code, both of which may influence the precision of the study findings. The severity of the disease was not recorded in detail. As comorbidities were identified using ICD-9 CM codes, certain comorbidities may have been underestimated or overestimated. The population included in the database had commercial and Medicare supplemental insurances and may not be comparable to the general population in all characteristics. We also were not able to include costs for medical services that may have been needed but were not covered by the benefit plan in this database. Such supplementary services would have incurred out-of-pocket expenses for patients.

Finally, the work centered on a US population and costs were calculated according to US data. The ability to extrapolate these figures to other countries, healthcare systems and

sIBM populations may be limited, although the economic burden associated with sIBM relative to the general population can be expected to be substantial in most developed economies.

In summary, this study demonstrates the high burden of illness in patients with sIBM. The burden is reflected in substantial additional healthcare utilization needs and associated costs incurred by patients in a US setting. Further cost analyses from different countries and healthcare systems, as well as more epidemiological investigations into sIBM would greatly improve our knowledge of the personal and societal costs of this debilitating disease.

Tables

Table 1. Demographic characteristics of the study populations at index date (at baseline for comorbidities), matched on age and sex

Characteristic	sIBM (n=333)	Matched cohort (n=1665)
At index date		
Mean age (SD)	69 (9.6)	69 (9.6)
50 – 64	41%	41%
65 – 79	42%	42%
80+	17%	17%
% Male	66%	66%
Plan Type		
Fee for service	86%	83%
HMO and POS capitation	12%	14%
Unknown	2%	3%
Charlson comorbidity index at baseline mean ±SD*	1.8 ±1.9	1.1 ±1.7
Medication burden † at baseline mean ±SD*	6.9 ±6.4	5.5 ±5.2

* p-value <0.05 for differences between the groups

† Mean number of Uniform System of Classification (USC) medications taken at baseline

HMO, Health Maintenance Organization; POS, Point Of Service; sIBM, sporadic Inclusion Body Myositis

Table 2. Adjusted annual total healthcare utilization costs in United States Dollars (USD) for sIBM patients and control patients

Healthcare-resource cost	sIBM patients n=333, Mean (SD), % all cause healthcare costs	Control patients n=1665, Mean (SD)	Adjusted mean cost difference (95% confidence interval)*
Emergency room (USD)	765 (133)	473 (49)	292 (110, 741)
Inpatient (USD)	4897 (765)	2809 (311)	2088 (428, 4034)
Outpatient visits (USD)	19,337 (2131)	6432 (557)	12,906 (9579, 17,926)
All-cause medical costs[#] (USD)	30,347 (3832)	11,512 (1488)	18,835 (12,765, 25,388)
Outpatient Prescription drugs (USD)	4521 (890)	2548 (224)	1973 (347, 3844)
All cause healthcare costs[$] (USD)	33,259 (3541)	13,870 (1290)	19,389 (12,855, 26,763)

* = Adjusted for age, sex, region, insurance type, sIBM-related conditions, Charlson index score, baseline medication burden and baseline healthcare utilization

[#] including ER costs, inpatient and outpatient visits cost

[$] including all cause medical costs and outpatient prescription drug costs

List of Abbreviations

CCI	Charlson Comorbidity Index
CIs	Confidence Intervals
ER	Emergency Room
HCL	Hydrochloride
HMO	Health Maintenance Organization
ICD-9 CM	International Classification of Diseases – Clinical Modification, Ninth Revision
IRR	Incidence Rate Ratio
MRI	Magnetic Resonance Imaging
PEG	Percutaneous endoscopic gastrostomy
POS	Point Of Service
QoL	Quality of Life
SF-36	36 questions Short Form questionnaire
sIBM	sporadic Inclusion Body Myositis
sIFA	sporadic Inclusion Body Myositis Physical Functioning Assessment
SD	Standard Deviation
US	United States

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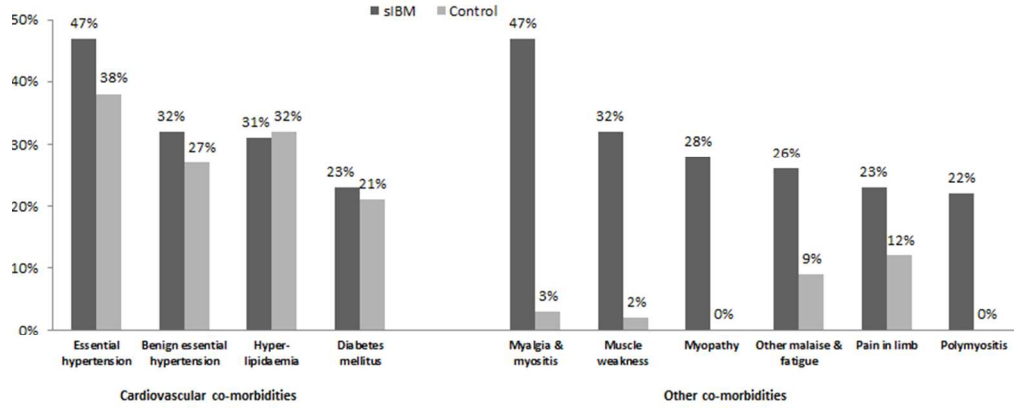
Figures

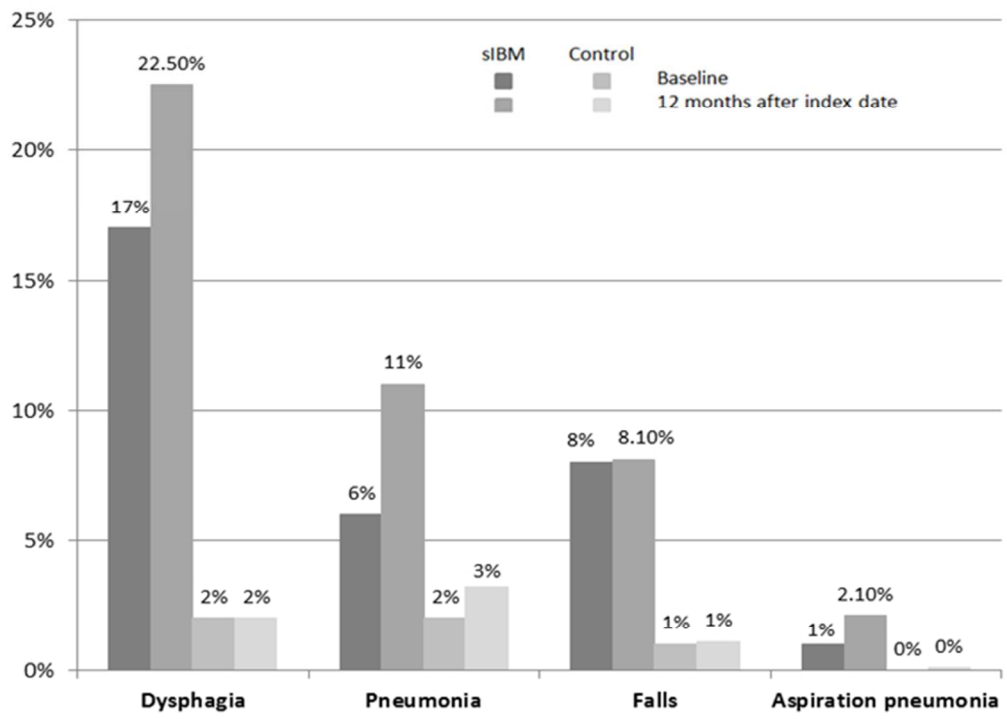
Figure 1. The most frequent comorbidities in sIBM patients at baseline compared with rates in the control patient population

Figure 2. Rates of sIBM-related conditions in the period between baseline and index date, and in the 12 months after the index date, respectively. The control group is shown in light orange for the period between baseline and index date and dark orange for the 12 months after the index date. sIBM patients are shown in light blue for the period between baseline and index date and dark blue for the 12 months after the index date. All differences between the sIBM cohort and the control population were statistically significant at $p<0.0028$



The most frequent comorbidities in sIBM patients at baseline compared with rates in the control patient population

222x98mm (96 x 96 DPI)



Rates of sIBM-related conditions in the period between baseline and index date, and in the 12 months after the index date, respectively. The control group is shown in light orange for the period between baseline and index date and dark orange for the 12 months after the index date. sIBM patients are shown in light blue for the period between baseline and index date and dark blue for the 12 months after the index date. All differences between the sIBM cohort and the control population were statistically significant at $p<0.0028$

193x141mm (96 x 96 DPI)