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Applying sequence clustering techniques to explore practice-based ambulatory care pathways in insurance claims data

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Background: Care pathways are a widely used mean to ensure well-coordinated and high quality care by defining the optimal timing and interval of health services for a specific indication. However, evidence on common sequences of services actually followed by patients has rarely been quantified. This study aims to explore whether sequence clustering techniques can be used to empirically identify typical treatment sequences in ambulatory care for heart failure (HF) patients and compare their effectiveness. **Methods:** Routine data of HF patients were provided by a large statutory sickness fund in Germany from 2009 until 2011. Events were categorized by either (i) the specialty of the physician, (ii) the type of service/procedure provided and (iii) the medication prescribed. Similarities between sequences were measured using the 'longest common subsequence' (LCS). The k-medoids clustering algorithm was applied to identify distinct subgroups of sequences. We used logistic regression to identify the most effective sequences for avoiding hospitalizations. **Results:** Treatment data of 982 incident HF patients were analyzed to identify typical treatment sequences. The cluster analysis revealed three distinct clusters of specialty sequences, four clusters of procedure sequences and four clusters of prescription sequences. Clusters differed in terms of timing and interval of physician visits, procedures and drug prescriptions as well as comorbidities and HF hospitalization rates. We found no significant association between cluster membership and HF hospitalization. **Conclusions:** Sequence clustering techniques can be used as an explorative tool to systematically extract, describe compare and analyze treatment sequences and associated characteristics.

Introduction

Chronic diseases are the leading cause of the worldwide burden of disease and represent one of the greatest challenges faced by many health systems around the globe.[1,2] Chronic disease management requires coordination of various inputs from several health providers and continuous monitoring over an extended period of time to ensure high quality care and avoid duplication of diagnostic testing, polypharmacy and conflicting care plans.[3,4]

The most popular approaches to chronic disease management include clinical guidelines and care pathways or care maps.[5] Clinical guidelines use evidence-based medicine and consensus procedures to give recommendations for the appropriate and effective care including prevention, diagnostics, treatment, and long-term management for a specific condition. As most of these guidelines do not give recommendations regarding the optimal interval and timing of the services, they are often translated into care pathways or care maps that define the ideal sequence of essential steps in the care of patients with a specific disease or indication.[6] Most of the existing care pathways, however, focus on services within a clinic or a specific organization[7] as care for these services has only a limited time frame and is more easily predictable than care in the ambulatory sector where different health professionals intervene both simultaneously and consecutively.[8] Furthermore, recommendations regarding the sequence of care are mostly based on consensus-based decisions as there is a lack of evidence on effective treatment sequences.[9]

Data-driven techniques can potentially support the empirical identification of effective care sequences by extracting them from data collected routinely in health care. Applied to event data recorded in health care information systems, techniques such as sequence clustering can assess frequently performed medical behavior and the chronological sequence of these behaviors. Thereby, these techniques could provide insights on the interval and timing of treatment patterns used in practice and the effectiveness of different treatment sequences. This knowledge could be used for (re)designing and/or optimizing existent care pathways.[10]

Only few studies applied such techniques to data generated in the ambulatory sector where comprehensive data is often unavailable. Lakshmanan et al.[11] used sequence clustering algorithms to mine practice-based care pathways of one US healthcare provider and rank them according to their correlation with particular patient outcomes. Zhang et al.[9] extracted common pathways based on electronic health record data of chronic kidney disease patients obtained from one community nephrology practice.

To the best of our knowledge, none of the previous studies covers the care delivery pathway between different providers in the ambulatory sector. The aim of this study is, therefore, to explore whether sequence clustering techniques combined with a heuristic approach for extracting representative pathways can be used to empirically identify and describe common ambulatory care pathways between different providers. Using German statutory health insurance (SHI) claims data of heart failure (HF) patients, we extract typical care delivery pathways while considering transitions between physicians. In addition, we analyze whether the extracted pathways are associated with hospitalization to identify effective care delivery pathways.

We use HF as indication to empirically model ambulatory care pathways because it is a chronic disease with epidemiological significance and a high potential for cost reductions. It has been estimated that 64% of HF hospitalizations could be prevented by timely and effective care of the chronic condition in the ambulatory sector.[12]

Methods

Data

This study used anonymized claims data provided by the regional SHIs ‘Allgemeine Ortskrankenkassen’ (AOKs) from 2009 to 2011. In Germany, about 86% of the population receives coverage for a comprehensive benefits catalogue by SHI. The AOKs provide health insurance for ∼24 million persons (∼1/3 of the total population) and routinely collect data about their hospital stays, physician visits, medication and diagnoses. We identified 1 575 144 patients aged 35 years or older with at least one diagnosis of HF in 2010 (ICD-10 I10.0, I13.0, I13.2, I50.x). From the identified patients a random sample of 500 014 patients was drawn and used in our analysis. We restricted our analysis to patients with left ventricular failure in class II (ICD-10 I50.12) according to the New York Heart Association (NYHA) Functional Classification in order to ensure that the pathways are not biased by different degree of severity. In addition, we only included patients with an index diagnosis of HF in the first quarter of 2010 not preceded by a HF diagnoses in 2009 to focus on ambulatory care pathways for incident HF patients and to ensure an observation period of two years (8 calendar quarters) ($n = 1{,}577$).

We excluded patients who died in the observation period ($n = 179$) and patients with <300 insurance days in each year of the observation period ($n = 14$) to ensure a complete history of our sample’s utilization pattern. Additionally, we excluded patients diagnosed with cancer ($n = 275$), diabetic foot ($n = 168$), and dialysis patients ($n = 25$).

Pathway construction

Each patient’s claims data recorded in a period of 24 months after the index diagnosis were considered in the pathway mining process. Data were assessed in a quarterly period because basic services including personal doctor–patient contacts are covered by a per capita payment that is only billed at the first visit in a quarter in Germany. The quarters were chronologically sorted and categorized by information on health care services used by each patient that are associated with HF. The quarters were categorized by specialty of the physicians visited in each quarter, medication prescribed and procedures performed that are relevant for HF care.

We constructed three different types of sequences so that each patient’s visit history is represented by three sequences (see table 1 for an overview): In the *first* type of sequences we included services/procedures recommended by guidelines for HF care, such as the National Disease Management Guideline for Heart Failure (Germany) and the guideline of the European Society of Cardiology.[13] According to these guidelines, echocardiography is recommended for diagnosing HF.[14] In addition, it is recommended to control renal function and serum electrolytes in half-yearly periods.[15] Thus, we categorized quarters by the following services: Electrocardiogram (ECG), Echocardiography (Echo), and/or laboratory tests of renal function and serum electrolytes (lab).

Table 1 Items considered per quarter in the construction of the sequences

Specialty sequence		Procedure sequence		Medication sequence	
GP	General practitioner	ECG	Electrocardiogram	ACE_ARB	ACE hemmer, or ARB
IM	Internist	ECH	Echocardiography	Beta	Beta-blocker
C	Cardiologist	Lab	Laboratory test		

ACE: Angiotensin converting enzyme; ARB: Angiotensin-II-receptor type 1.

According to the guidelines, patients with HF are assumed to benefit from regular follow-up visits with a physician to ensure the safety and optimal dosing of medicines and detect the development of complications or disease progression that may require a change in management.[14] We, therefore, considered a *second* type of sequences indicating whether a personal doctor-patient contact was billed by an office-based physician who is generally involved in patient care for HF and provides care for patients in SHI. As Cardiologists report practices more in conformity with published guidelines for HF than internists and GPs,[16] we categorized the quarters by the specialty of the physician who billed a service in the quarter: GPs, Cardiologists (C) and Internists (IM).

In the *third* type of sequences quarters were categorized by indicating whether a medication recommended for symptomatic HF patients with reduced ejection fraction was prescribed. An angiotensin converting enzyme (ACE) hemmer and a β-blocker is recommended for symptomatic patients with HF to reduce mortality rates, hospitalization, and morbidity in HF.[14,17,18] Angiotensin receptor blockers (ARB) are recommended when patients are intolerant for ACE hemmer.[13]

Analysis

The aim of the analysis is to identify subgroups of patients that share common sequences. The analysis consists of five steps: First, the longest common subsequence (LCS) between the patient sequences was measured according to Elzinga.[19] LCS is the maximum number of events two sequences have in common while preserving the order of occurrence:

$$LCS(x, y) = \max\{|u| : u \in S(x, y)\}$$

Where $|u|$ is the length of the subsequence for the pair of sequences (x, y) out of the nonempty set of subsequences $S(x, y)$ of sequences x and y.

In the second step, the distance between each patient's sequence and all other sequences was measured. The distance measure is defined as the length $|x|$ of sequence x and length $|y|$ of sequence y minus twice the LCS.

$$dLCS(x, y) = |x| + |y| - 2LCS(x, y)$$

Third, the k-medoids clustering algorithm was applied to identify subgroups of patients that share common sequences. The clustering algorithm is based on the distance measure defined above. The number of clusters (k) was determined using the silhouette approach.

In the fourth step, we extracted representative pathways for each cluster using a heuristic proposed by Gabadinho et al.[20] Therefore, a representativeness score was computed for each distinct sequence in the dataset according to its neighborhood density. Neighborhood density was measured as the number of sequences in the neighborhood of each distinct sequence. The neighborhood ratio (i.e. the percentage of the maximum theoretical distance between two sequences) was set to 10%. For measuring the distances and extracting representative pathways the TraMineR package in R (version 3.4.0) was used. We visualized the representative pathways using the ggplot2 package in R.[21]

We calculated summary statistics for each of the identified clusters to compare differences with regard to comorbidities, hospital admissions and ambulatory care costs. Ambulatory care costs were calculated by summing up the number of points billed for each patient according to the Physicians' Fee Schedule (Einheitlicher Bewertungsmaßstab - EBM) and multiplying it by the so-called point value (Orientierungspunktwert). The chi-squared test was used to compare differences in categorical variables and one-way ANOVA to compare continuous variables between clusters.

In a last step, we estimated a logistic regression model to assess whether there is a significant correlation between cluster membership and hospitalizations in 2011 with HF as discharge diagnosis controlling for age, sex and comorbidity. HF hospitalization is often referred to as an indicator for the quality of ambulatory care[22] and is considered to be potentially avoidable through timely and effective ambulatory care.[23,24] In the model, we controlled for the patient's age and sex (1 = male; 2 = female) and the Charlson comorbidity index based on ICD-10 codes.[25] The model was fitted using maximum likelihood estimation with robust standard errors in STATA (version 12.1).

Results

After applying the entry criteria for this study, a total of 982 eligible patients were identified from the data. Characteristics of the study sample are listed in Supplementary table S1.

The cluster algorithm based on the distance between the sequences revealed 4 procedure sequence clusters with an average silhouette width of 0.33, 3 specialty sequence clusters with an average silhouette width of 0.44 and 4 medication sequence clusters with an average silhouette width of 0.47. In figure 1, for each cluster, the 10 most representative sequences with highest density are plotted bottom up according to their representative score. The bar width is proportional to the number of sequences assigned to each representative.

Patients in *procedure sequences* cluster 4 usually had an echocardiography in the first quarter (figure 1). In procedure sequence cluster 1 laboratory examinations were conducted in nearly every quarter and cluster 4 was characterized by regularly conducted echocardiographs whereas cluster 3 showed an absence of laboratory examinations. *Physician specialty sequence* clusters differed with regard to whether only a GP or also an internal specialist or a cardiologist was visited to manage HF. In all specialty clusters a high proportion of sequences were characterized by a cardiologist visit in the first quarter (initial diagnosis of HF). In *medication sequences cluster* 1 prescriptions of ACE/ARB were issued almost every quarter. Patients in medication cluster 2 received prescriptions only for β-blockers in regular intervals. Medication cluster 3 was characterized by an absence of regular prescriptions.

Summary statistics of patient characteristics by clusters are listed in table 2. Procedure cluster 1 had the highest average ambulatory care costs compared to the other procedure clusters. The number of quarters with a cardiologist visit was highest in procedure cluster 4. Patients in specialty cluster 1, with regular cardiologist visits, were more likely to be male than patients in the other specialty clusters. Specialty cluster 1 had a higher share of patients with laboratory examinations and echocardiographs. Medication clusters differed with regard to patients comorbidities. In medication cluster 3, the prevalence of renal insufficiency was lowest whereas in cluster 2 prevalence of asthma was lower compared to the other medication clusters.

Table 3 reports the exponentiated coefficients and 95% confidence intervals of the logistic regression for HF hospitalization. Adjusting for the contributions of the other variables in the model there was no significant difference in HF hospitalization between clusters for all three types of sequences. As expected, the Charlson index was positively and significantly associated with a HF hospitalization (OR 1.33, $P < 0.01$).

Discussion

In this explorative study, we examined whether sequence clustering techniques could be used to empirically identify typical treatment sequences in ambulatory care for HF patients and compare their effectiveness. We explored common ambulatory care pathways at the quarterly level including transitions between cardiologists, GPs and internists as well as different procedures and medications prescribed for HF patients.

We identified different empirical patterns of health care sequences among HF patients by means of sequence clustering techniques. Cluster analysis of *procedure sequences* identified differences in

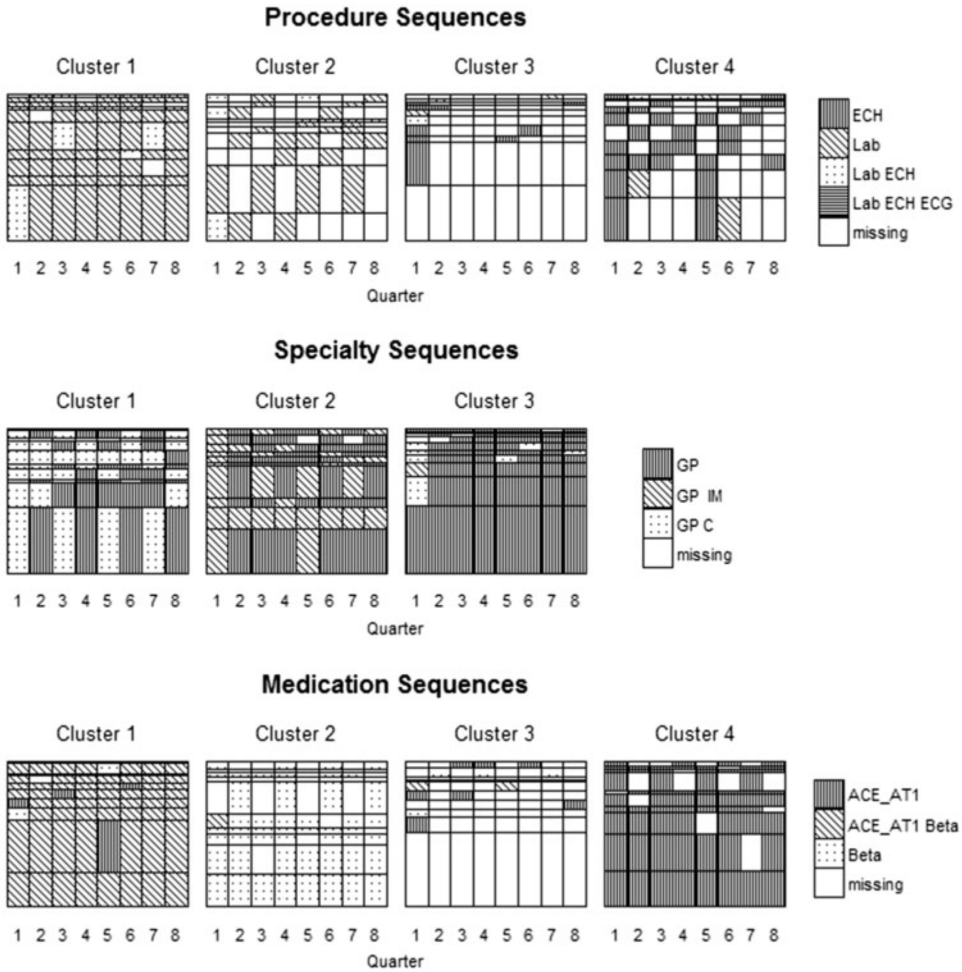

Figure 1 Representative sequences for each cluster within procedure, specialty and medication sequences. The 10 most representative sequences in each cluster with highest neighborhood density are plotted bottom up according to their representative score. The neighborhood ratio (i.e. the percentage of the maximum theoretical distance between two sequences) was set to 10%. The bar width is proportional to the number of sequences assigned to each representative. The acronyms used in the figure are explained in table 1

terms of the number and intervals of laboratory examinations and echocardiography or ECGs. For example, cluster 1 and 2 had the highest utilization of laboratory tests in almost every quarter (cluster 1) or in less frequent intervals (cluster 2). In addition, cluster 4 of procedure sequences with a high utilization of echocardiographs and cluster 1 of specialty sequences (high number of cardiologist visits) were highly correlated (correlation coefficient = 0.37, Supplementary table S2). The clusters also differed in terms of patient characteristics. For example, patients in cluster 4 with a high utilization of echocardiography were more likely to be male than patients in the other clusters. In cluster 1 and 2 with the highest utilization of laboratory tests the prevalence of diabetes mellitus and renal insufficiency was higher.

The identified *specialty sequences* differed in terms of the timing and interval of physician specialty visits, for example quarterly, half-yearly, or no visits to a cardiologist or internist in addition to a GP. In addition, specialty sequences differed in terms of procedures used. For example, patients with a regular cardiologist follow-up were more likely to undergo echocardiography than patients who only visited a GP or an internist. This pattern was also found by a previous study on differences in the management of HF between cardiologists and internists.[26] A possible explanation for the less frequent use of echocardiography by GPs could be that internists and GPs have limited access to these tests. There were no significant differences between specialty sequences clusters with regard to patient comorbidity.

Medication sequences differed in terms of whether patients received prescriptions for β-blocker and/or ACE/ARB. In addition, there were differences with regard to the interval of prescription issuing between and within clusters. Whereas in some sequences a HF medication was prescribed every quarter, other patients received a prescription only in every second quarter. In addition, the clusters were characterized by different comorbidities. Cluster 3 had the lowest proportion of patients who receive HF medication and at the same time the lowest proportion of patients with hypertension and renal insufficiency.

The findings of the clustering analyses should be interpreted in the light of the characteristics of the German health care system in order to understand the differences in the identified sequences. In Germany, patients are free to select a physician of their choice as there is no traditional gate-keeping system in the ambulatory care sector. Thus, patients can consult different GPs and specialists on the same medical problem simultaneously. This could be one possible explanation for the high number of cardiologist visits in the specialty sequence cluster 1. In addition, there is no electronic medical record system in Germany that informs physicians about test results patients receive from other physicians. This may lead to performing unnecessary diagnostic tests and could explain the high volume of echocardiographs conducted in procedure cluster 4.

We performed a logistic regression analysis to assess whether the differences in the sequences are associated with HF hospitalization. Although previous studies found significant differences between

Table 2 Unadjusted summary statistics by sequence clusters

	Physician specialty pathway clusters				Procedure pathway clusters					Medication pathway clusters				
	CL 1	CL 2	CL 3	*P* value	CL 1	CL 2	CL 3	CL 4	*P* value	CL 1	CL 2	CL 3	CL 4	*P* value
n	242	134	606		119	209	539	115		475	123	143	241	
Age (mean)	69.81	71.63	72.27	0.011	71.94	72.00	71.89	68.94	0.051	71.28	72.07	70.55	72.54	0.284
Sex (% Women)	39.67	56.72	61.55	<0.001	49.58	60.29	58.07	40.87	0.002	53.68	57.72	60.84	54.77	0.461
Physician group (mean no. of quarters)														
GP visit	7.51	7.46	7.84	<0.001	7.93	7.80	7.58	7.90	<0.001	7.80	7.82	7.10	7.83	<0.001
Cardiologist visit	4.17	0.55	0.80	<0.001	1.96	1.41	1.15	3.64	<0.001	1.81	1.46	1.08	1.55	<0.001
Internist visit	0.48	3.68	0.24	<0.001	0.87	0.94	0.60	1.15	<0.001	0.81	0.63	0.76	0.76	0.707
Procedures (% patients)														
Laboratory examination	71.90	67.16	57.26	<0.001	100	100	39.52	60.87	<0.001	62.53	61.79	57.34	64.73	0.547
Echocardiography	94.63	80.60	57.43	<0.001	73.11	70.81	62.15	100	<0.001	74.74	65.04	62.94	66.39	0.010
ECG	15.70	20.15	13.86	0.179	18.49	19.62	11.32	21.74	0.003	17.05	10.57	13.29	14.94	0.292
Medication (% patients)														
ACE/ARB	88.84	88.06	83.83	0.118	82.35	91.39	82.93	91.30	0.005	100	51.22	43.36	100	<0.001
β-blocker	78.10	70.90	71.45	0.121	76.47	73.21	70.13	82.61	0.039	100	100	30.77	31.12	<0.001
Comorbidities (% patients)														
Hypertension	92.15	94.03	91.58	0.637	93.28	91.39	91.28	95.65	0.416	96.21	90.24	76.22	94.19	<0.001
Renal insufficiency	18.18	26.12	19.97	0.173	33.61	28.23	15.40	15.65	<0.001	24.42	20.33	8.39	19.50	0.001
Diabetes mellitus	41.32	53.73	47.85	0.057	74.79	52.63	41.74	33.04	<0.001	50.53	44.72	42.66	43.98	0.204
COPD	27.27	20.15	21.78	0.163	24.37	25.84	21.52	22.61	0.625	19.58	13.01	29.37	30.71	<0.001
Asthma	11.57	8.21	11.06	0.570	11.76	10.05	10.95	10.43	0.966	8.42	4.88	11.89	17.84	<0.001
Angina pectoris	3.31	2.24	2.81	0.833	3.36	1.91	2.97	3.48	0.810	3.37	1.63	2.80	2.49	0.743
Charlson index (mean)	2.60	2.81	2.21	0.051	2.91	2.94	2.03	2.50	<0.001	2.47	2.90	2.06	2.15	0.068
Hospitalized with HF as discharge diagnosis in 2011 (% patients)	3.31	5.97	3.96	0.445	5.04	5.74	2.41	7.82	0.021	5.05	4.88	2.10	2.90	0.303
Ambulatory costs (mean)	1528.79	1339.42	1184.93	<0.001	1556.81	1363.32	1157.33	1508.88	<0.001	1272.52	1254.79	1235.52	1377.81	0.182

ACE: Angiotensin converting enzyme; ARB: Angiotensin-II-receptor type 1; CL: Cluster; COPD: Chronic obstructive pulmonary disease; ECG: Electrocardiogram; HF: Heart failure; SD: Standard deviation.

Table 3 Logistic regression coefficients of the association between cluster membership and hospitalization ($N=982$)

	HF hospitalization OR (95% CI)
Specialty sequences	
Cluster 1	*Reference*
Cluster 2	2.126 (0.653–6.920)
Cluster 3	2.177 (0.711–6.670)
Procedure sequences	
Cluster 1	*Reference*
Cluster 2	1.101 (0.360–3.361)
Cluster 3	0.574 (0.202–1.633)
Cluster 4	3.663* (0.987–13.597)
Medication sequences	
Cluster 1	*Reference*
Cluster 2	0.692 (0.253–1.894)
Cluster 3	0.420 (0.123–1.430)
Cluster 4	0.556 (0.220–1.408)
Control variables	
Age	1.058** (1.009–1.111)
Sex	1.191 (0.527–2.691)
Charlson index	1.333*** (1.227–1.448)
Constant	0.000*** (0.000–0.004)
ll	−136.164
Pseudo R^2	0.185

***: $P<0.001$.
**: $P<0.005$.
*: $P<0.01$.
CI: Confidence Interval, ll: log-likelihood, OR: Odds ratio.

cardiologists, GPs and internists with regard to guideline recommendations[16] and hospital readmission,[27] we found no significant differences in the odds for HF hospitalization between physician specialty sequences. Furthermore, we found no significant differences between sequences with regularly conducted laboratory tests or echocardiographs and pathways without regular examinations and between medication sequences.

The following limitations have to be considered when interpreting the results of the sequence clustering analyses: First, the study is based on data collected routinely in health care for billing and reimbursement purposes. Due to the per capita payment of basic services that is only billed at the first visit in a quarter in Germany's ambulatory care sector we were not able to construct the pathways on a more detailed temporal level such as months or days. However, a more detailed temporal ordering could help to accurately learn the co-progression and temporal relationship of health care services utilization and outcomes.[9] In addition, we have chosen to limit the observation period to two years because this enabled a clear presentation of the different sequences within and between the clusters. Although we wouldn't expect the observed patterns to change considerably, further analysis should apply the sequence clustering techniques to a longer observation period to compare the long-term effects of different treatment sequences. Second, events within a sequence were only categorized by information on procedures, medication prescription and physician specialty. We did not consider patient characteristics, such as disease progression or comorbid conditions in the clustering algorithm. In order to ensure that the pathways are not biased by varying degrees of severity, we excluded 498 437 patients that either had no record of the ICD I50.12 in the first quarter of 2010 or had a previous diagnosis of heart failure in 2009. The main reason for the large number of patients that met the exclusion criteria is that physicians in ambulatory care in Germany often only record the ICD I51.9 or I50.19 rather than the ICD codes that classify the severity of heart failure according to the NYHA (I50.11–I50.14). Further analyses should focus on controlling for the progression of the disease in the sequence clustering algorithm to allow for including a larger sample of patients with different degrees of severity and different comorbidity. Third, the average silhouette width ranged between 0.33 and 0.47 suggesting that the structure of the clusters was not very strong. The visualization of the representative sequences in each cluster however underlines that there were substantial differences in the sequences between clusters.

Fourth, we extracted representative sequences to exhibit the key features of the clusters. As a consequence, infrequent pathways were missing in the presentation. Fifth, the confidence intervals of the odds ratios were relatively large indicating a low statistical power of the estimated logistic regression and, accordingly, a high probability for a type II error. Thus, further studies are needed to re-evaluate this association with a larger sample size. Sixth, the generalizability of our results to the general population in Germany is limited due to the specific age- and sex-structure of the population covered by the AOKs. For instance, the prevalence of heart failure is estimated one percentage point higher in the AOK population than in the German population.[28]

Conclusion

Different subgroups of common ambulatory care pathways among HF patients can be identified by means of sequence analysis techniques. The subgroups identified varied in terms of care delivery patterns such as timing and interval of procedures, medications and physician specialty visits. These variations could be due to variations in comorbidity and thus reasonable or due to unwarranted variations in service delivery. We found no correlation between different subgroups of ambulatory care pathways and hospitalization for HF. However, sequence clustering techniques could be used as an explorative tool to extract and describe common care pathways and analyze associated characteristics. Thereby, these techniques could support the monitoring of guidelines that suggest specific patterns of health service delivery, especially if the analysis is provided with more detailed data.

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Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interest: None declared.

Key points

- We explore whether sequence clustering techniques can be used to empirically identify typical treatment sequences.
- Cluster analysis revealed different patterns of treatment sequences.
- The identified sequences differ by timing and interval of health services delivery.
- Sequence clustering techniques are a useful tool to systematically extract, describe and compare treatment sequences.

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