Journal of Clinical Epidemiology 109 (2019) 42–50

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Medical diagnoses showed low relatedness in an explorative mutual information analysis of 190,837 inpatient cases

Jan A. Roth[a,b,c,1], Thomas Sakoparnig[c,d,e,1], Simon Neubauer[c,f], Eleonore Kuenzel-Pawlik[c,f], Martin Gerber[c,g], Andreas F. Widmer[a,c], Balthasar L. Hug[c,h,*], the PATREC Study Group

[a]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland
[b]Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Spitalstrasse 12, 4031 Basel, Switzerland
[c]University of Basel, Petersplatz 1, 4001 Basel, Switzerland
[d]Focal Area of Computational and Systems Biology, Biozentrum University of Basel, Klingelbergstrasse 70, 4056 Basel, Switzerland
[e]SIB Swiss Institute of Bioinformatics, Quartier Sorge—Batiment Genopode, 1015 Lausanne, Switzerland
[f]Analytics Unit, Department of Finance, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland
[g]Department of Finance, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland
[h]Department of Internal Medicine, Kantonsspital Luzern, Spitalstrasse, 6000 Lucerne, Switzerland

Accepted 8 January 2019; Published online 11 January 2019

Abstract

Objectives: We aimed to quantify the shared information between medical diagnoses of an adult inpatient population to explore both multimorbidity patterns and vice versa the unrelatedness of medical diagnoses.

Study Design and Setting: This was a cross-sectional study, performed at a tertiary care center in Switzerland. Diagnoses were routinely coded using the International Classification of Diseases, 10th revision.

Results: Among 190,837 inpatient cases, 7,994 unique diagnoses were coded. There were 31.9 million possible diagnosis pairs; the respective mutual information scores in diagnosis pairs were low (range, 10^{-7} to 0.237). There were 148 pairs of diagnoses with a mutual information score higher than 0.01, which formed several clinically plausible disease clusters; 27.2% of cases did not have a diagnosis that belonged to one of the morbidity clusters.

Conclusion: In an explorative analysis, we observed a high unrelatedness of diagnoses in a tertiary-care inpatient population. This finding indicates that although multimorbidity patterns can be observed, inpatient cases frequently have further, unrelated diagnoses, which share little information with specific other diagnoses. Therefore, management of multimorbid patients should be individualized and may not be generalized based on a few multimorbidity patterns or clusters.

Keywords: Co-occurrence; Electronic medical record; Entropy; International classification of diseases; Multimorbidity; Mutual information

1. Introduction

Multimorbidity—defined as the co-occurrence of two or more diseases in the same person—is increasing in prevalence worldwide because of growing longevity [1], which is related to improvements in prevention (including sanitation and nutrition) and in health care delivery [2,3]. This trend toward co-occurring and often chronic morbidities has a substantial medical and economic impact on societies, health care institutions, and patients [2–4].

Most health interventions target single diseases and respective medical guidelines and recommendations do often not account for multimorbidity, which can complicate treatment decisions in daily routine. In addition, focusing on single diseases may negatively affect health outcomes

Funding: This study project received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Conflict of interest statement: The authors have no competing interests in the work presented.

Authors' contributions: J.A.R., T.S., and B.L.H. contributed to the study conception. T.S. performed the main data analyses. J.A.R. and T.S. wrote the first manuscript draft. All authors contributed to interpreting the study findings and drafting the article. All authors reviewed and approved the final article.

[1] Shared first authors.

* Corresponding author: Tel.: +41 41 205 51 00; Fax: +41 41 205 51 82.

E-mail address: balthasar.hug@luks.ch (B.L. Hug).

https://doi.org/10.1016/j.jclinepi.2019.01.003

What is new?

Key findings

- As part of an explorative mutual information analysis, we observed a high unrelatedness of diagnoses in a tertiary-care inpatient population.

What this adds to what was known?

- This finding suggests that although multimorbidity patterns can be observed, inpatient cases frequently have further unrelated diagnoses, which share little information with specific other diagnoses.

What is the implication and what should change now?

- Management of multimorbid patients should be individualized and may not be generalized based on a few multimorbidity patterns or clusters.
- Mutual information may be a promising concept to characterize multimorbidity among different health care populations.

of multimorbid patients, which is driven by various mechanisms, for instance by causing co-occurring diseases to deteriorate or by leading to certain drug−drug interactions [2]. Therefore, to improve holistic patient management approaches and to reduce health care-associated complications, identification of multimorbidity patterns has become a key research priority [2,4]. To comply with the suggestions of committees such as the ‘‘Joint Action on Chronic Diseases’’ regarding the optimal treatment of multimorbid patients, data analyses of multiple diagnoses and their associations are required [5].

The increasing availability of electronic medical records and other routine data sources in health care allows studying high-dimensional co-occurrence patterns of diseases [4]. But to make clinical use of such information, clearly demarcated and generalizable multimorbidity patterns have to be detected; otherwise, treatment guidelines and recommendation may not be ‘‘streamlined’’ for patient categories with certain disease patterns. Consequently, from an information theoretical point of view, one could explore the mutual (i.e., shared) information between medical diagnoses to characterize multimorbidity patterns and to quantify the information entropy, that is unrelatedness, of medical diagnoses. Previous studies investigating multimorbidity patterns focused largely on specific patient populations (e.g., elderly patients, individuals with mental diseases) and yielded heterogeneous multimorbidity patterns with a few relatively consistent and clinically well-established disease combinations (e.g., metabolic syndrome) [4,6].

We therefore aimed to quantify the mutual information and unrelatedness of medical diagnoses in an adult inpatient population without restriction to specific diseases, medical disciplines, or age strata. Because of the explorative and high-dimensional nature of our study, we have decided a priori not to investigate (i) multimorbidity patterns by applying a specific error threshold for false positive results (i.e., associative multimorbidity) or (ii) causal multimorbidity.

2. Materials and methods

2.1. Study design and patient selection

We performed a cross-sectional study at the University Hospital Basel, a tertiary-care 850-bed hospital in Northwestern Switzerland with more than 1,000,000 ambulatory patient contacts and over 36,000 inpatient cases per year. Treatment services cover all major medical and surgical disciplines, including specialized centers for hematopoietic stem cell and kidney transplantation.

From January 2012 through December 2017, all inpatients aged ≥18 years on hospital admission were eligible for study inclusion. We excluded patients who declined participating in observational studies that make secondary use of their routine health data (i.e., general research consent). We defined inpatients as patients who were hospitalized for at least 24 hours.

The Ethics Committee of Northwestern and Central Switzerland approved this study project with a waiver of informed consent (project number 2016-02,128). We followed the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) recommendations for study reporting [7].

2.2. Data extraction and study definitions

A data manager extracted the relevant data of included patients on an inpatient case level (i.e., for each hospitalization period lasting from hospital admission to discharge) from an in-house in-memory data platform (SAP HANA; SAP AG, Walldorf, Germany), which is used as an analytical layer for high performance analyses that we described elsewhere [8]. After the anonymization of the study data and transformation of the data structure, no filtering was required, as the diagnoses were available for all eligible inpatient cases. We verified the completeness of the data extraction process by analyzing the yearly total case numbers and by performing further data quality checks.

Extracted structured diagnoses were coded by medical coders for billing and controlling purposes according to the ‘‘International Classification of Diseases, 10th revision’’ ([ICD-10]; German modification) and were based on the active discharge diagnoses of each inpatient case, which were present on hospital admission (e.g., previously diagnosed chronic diseases) or newly diagnosed during hospital stay. The respective treating senior physician verified all diagnoses before coding. Previous diagnoses that were no longer present during the respective hospitalization period (e.g., diagnosis of a tibia fracture 10 years ago) were not coded. No data linkage with other databases was performed. The investigators had full access to the complete database population.

We stratified health care disciplines into four categories based on the unit from which the inpatient was discharged, that is, surgery and orthopedics (i), medicine (ii), gynecology and obstetrics (iii), and other disciplines (iv) (e.g., ear, nose and throat clinic, eye clinic, human genetics, radiology).

2.3. Statistical analysis

2.3.1. Mutual information

To quantify the occurrence relationship between pairs of medical diagnoses (i.e., noncollapsed ICD-10 codes, as used previously in cluster analyses [4]), we calculated the mutual information scores between these diagnostic keys. Mutual information is a concept of information theory that quantifies the general interdependence (or vice versa unrelatedness) of two random variables [9]. Mutual information scores are more general than correlation coefficients and measure how similar the joint distribution of random variables, here the joint occurrence patterns of the two diagnoses, are to the product of the marginal distributions. To be precise, they quantify how much information about one random variable is obtained through the other. Mutual information scores are non-negative and in our case the information is quantified in bits because we used the logarithm with base two in calculating it. Furthermore, if the two random variables are statistically independent, that is, the two diagnoses are unrelated, the mutual information score is 0. Mutual information is symmetric, that is, the mutual information of diagnosis 1 and diagnosis 2 is the same as the mutual information of diagnosis 2 and diagnosis 1. The concept of mutual information is linked to that of (information) entropy of a random variable and describes the unpredictability or unrelatedness of a state/variable.

Because of the large sample size, stratification by sex and discipline was used to control for confounding effects between age (categories) and the average number of diagnoses, the number of informative diagnoses, and the number of diagnosis pairs with mutual information scores >0.01. We decided a priori not to perform these analyses for the ''other'' discipline because of the small sample size. We defined informative diagnoses as diagnoses that had at a minimum case frequency of 1.8%, to reduce the variability in the respective estimates. The subsampling analysis consisted of sampling cases without replacement and was restricted to medicine and surgery/orthopedics disciplines with increased caseloads for older inpatients.

We performed all statistical analyses using Python, version 3.6.4 (Python Software Foundation, Wilmington, DE, USA). The computation of mutual information scores for all 31.1 million diagnosis pairs was performed at the High Performance Computing Center of the University of Basel (scicore.unibas.ch) and consumed a total central processing unit time of 73 days and 7 hours.

2.3.2. Multimorbidity patterns

As an approximation and for better interpretability, we filtered all mutual information scores between diagnosis pairs with a cutoff of 0.01. Mutual information cutoffs ≤ 0.01 led to an abundance of clinically implausible diagnosis pairs and patterns. The cutoff of 0.01 was deemed to be appropriate as part of an explorative analysis. We graphed all diagnoses, which were present in at least one diagnosis pair, as vertices and the corresponding mutual information scores as edges (Fig. 1).

3. Results

During the 6-year study period, there were 198,972 inpatient cases overall. After having excluded 8,137 cases who declined the general research consent, we included 190,837 cases in the final analysis. Overall, 7,994 unique diagnoses were coded (median number of diagnoses per case, 5.0; interquartile range [IQR], 3−8); the median age of cases was 63.0 years (IQR, 45−76) with a median length of hospital stay of 4.0 days (IQR, 2−8; Table 1).

Overall, there were 31.9 million possible diagnosis pairs; the respective mutual information was relatively low for most diagnosis pairs with scores ranging from 10^{-7} to 0.237 (Fig. 2). We observed the highest mutual information score between the diagnosis ''pregnancy, 37th week to 41st week'' and ''birth of a living singleton''. There were 10,807 cases with ''pregnancy, 37th week to 41st week'' and 12,864 cases with ''birth of a living singleton'' and the overlap was 10,272 cases. The second highest pair with a mutual information score of 0.088 was between ''birth of a living singleton'' and ''secondary bradytocia'' (overlap of 4,257 cases).

The diagnosis pair with the lowest mutual information score, which still went into subsequent analysis, was ''bruise of the scalp'' and ''accident, not further specified'' with a mutual information score of 0.01 (overlap of 647 cases). In total, there were 148 diagnosis pairs (consisting of 133 unique diagnoses) with a mutual information score higher than 0.01; these pairs were all clinically plausible. The diagnostic pair ''chronic sinusitis frontalis'' and ''chronic sinusitis maxillaris'' exhibited a moderate mutual information score of 0.001. At a mutual information score of 0.0001 for ''psychological and behavioral disorders caused by alcohol: residual state and delayed psychotic disorder'' and ''other unspecified alimentary anemia'' (overlap of three cases) virtually no information was shared between the occurrence distributions of these diagnoses. This implies that these two diagnoses are virtually unrelated.

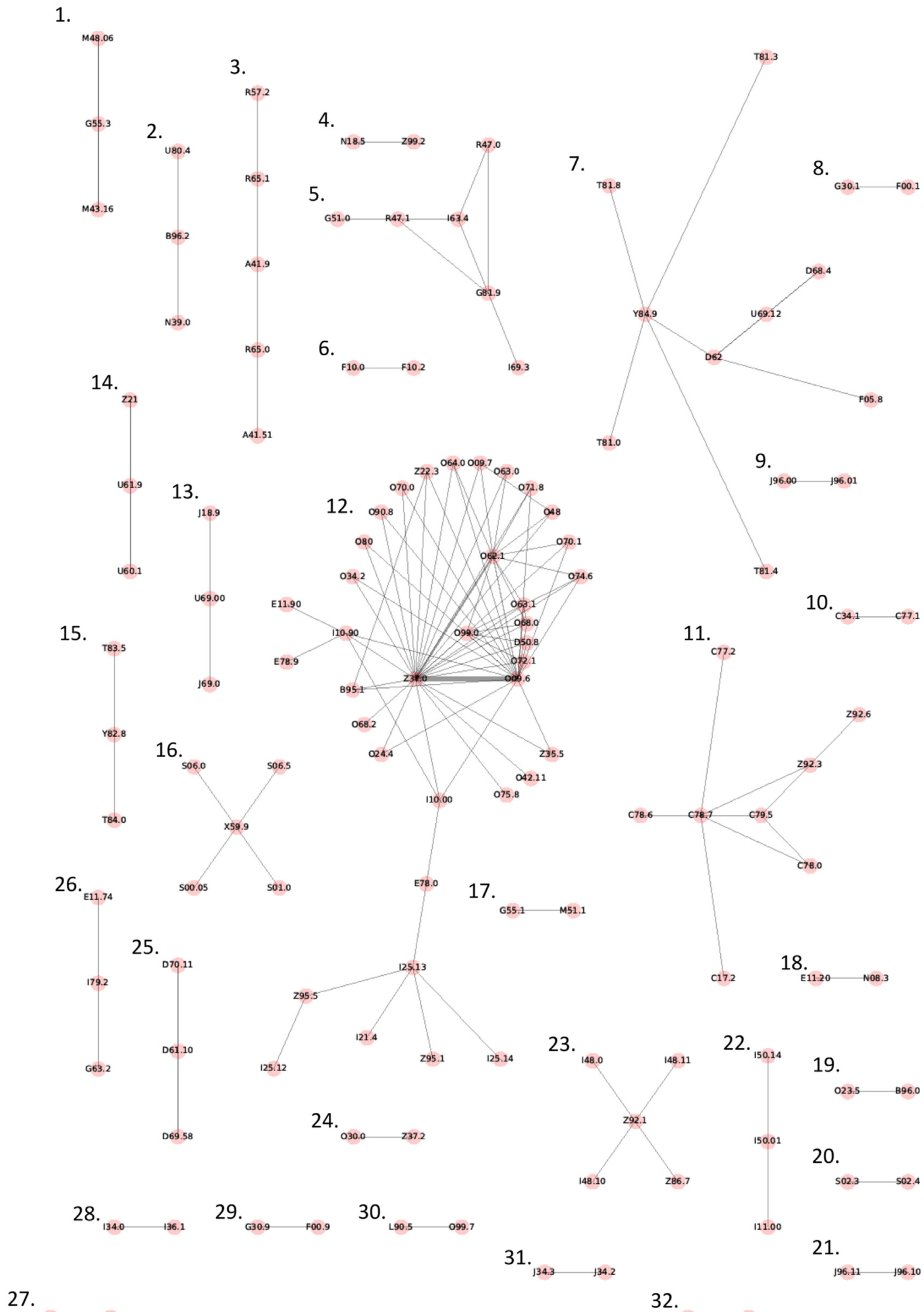

Fig. 1. Multimorbidity patterns (n = 190,837 inpatient cases). Descriptions of disease patterns with corresponding ''International Classification of Diseases, 10th revision'' codes are listed in the supplementum (Supplementary Text).

In the main ''medicine'' and ''surgery and orthopedics'' strata, the average number of diagnoses, the number of informative diagnoses, and the number of diagnosis pairs with a mutual information score >0.01 increased in higher age categories (Fig. 3); in contrast, in ''gynecology and obstetrics,'' the respective trends were not monotonic across

Table 1. Characteristics of the study population (n = 190,837 inpatient cases)

Parameter	Discharge discipline[a] All (n = 190,837 cases)	Discharge discipline[a] Medicine (n = 84,327 cases)
No. unique patients	114,651	53,972
No. cases per patient[b], mean	1.66	1.56
Case characteristics		
Age in years[c], median (IQR)	63 (45–76)	69 (55–79)
Female sex, n (%)	97,521 (51.1)	37,565 (44.6)
No. of diagnoses, median (IQR)	5 (3–8)	6 (3–9)
Cases with ≥2 diagnoses, n (%)	175,030 (91.7)	77,948 (92.4)
No. unique diagnoses	7,994	6,092
Top five diagnoses[d] (% of cases)	1. Essential hypertension, not further specified (14.0)	1. Essential hypertension, not further specified (18.5)
	2. Essential hypertension without hypertensive crisis (13.5)	2. Essential hypertension without hypertensive crisis (15.1)
	3. Diabetes mellitus type 2, without complications (8.8)	3. Hypokalemia (11.4)
	4. Accident, not further specified (8.2)	4. Any disease currently requiring anticoagulants (10.7)
	5. Hypokalemia (7.9)	5. Diabetes mellitus type 2, without complications (10.6)
Days of hospital stay, median (IQR)	4 (2–8)	3 (1–8)
In-hospital all-cause mortality, n (%)	3,834 (2.0)	2,615 (3.1)

Abbreviation: IQR, interquartile range.

[a] We stratified health care disciplines into four categories based on the unit from which the inpatient was discharged, that is, medicine, surgery and orthopedics, gynecology and obstetrics, and other disciplines (i.e., ear, nose and throat clinic, eye clinic, human genetics, pathology, and radiology).

[b] Within the study period.

[c] At hospital admission.

[d] Descending order according to overall frequency of diagnosis (per stratum).

age categories (Fig. 3). The results were consistent with subsampling, accounting for the increased caseload at higher age categories in medicine and surgery (Supplementary Fig. 1).

When applying a mutual information threshold of >0.01, we observed several well-established morbidity patterns in the overall case group (Fig. 1); the most prominent disease cluster (number 12) incorporated pregnancy- and birth-related conditions that branched out to a wide spectrum of diagnoses. Surprisingly, we observed a cluster (number 7), which included different surgical complications such as postoperative infections, delir, hemorrhage and hematoma, and other incidents; this cluster was not linked to any specific surgical site. Overall, 72.8% of cases had at least one diagnosis belonging to one of the depicted morbidity patterns. This implies that 27.2% of cases did not have a diagnosis that belongs to one of the morbidity clusters. In the 175,030 cases with at least two diagnoses (median number of diagnoses, 5; IQR, 3–8), 95.6% had at least one diagnosis, which did not belong to one of the disease clusters. Furthermore, of those 175,030 cases, 20.9% had no diagnosis belonging to these clusters.

4. Discussion

In this study, we have explored the mutual information and unrelatedness of medical diagnoses in a large inpatient population. We observed a high information entropy (i.e., unrelatedness) of diagnoses with only a few diagnosis pairs having a relatively high mutual information score, forming well-established disease patterns and clusters. To our knowledge, this is the first study in which mutual information analysis has been applied to quantify the amount of shared or vice versa unrelated information between medical diagnoses. Usage of mutual information allows quantification of the reduction of uncertainty about the state of one diagnosis if we know the state of the other diagnosis in a pair. As a measure of symmetry, it can be used for grouping diagnoses into clusters.

Our study findings shed light on the common unrelatedness or—statistically speaking—entropy of medical diagnoses. In our study, around 27% of cases did not have a diagnosis that belongs to one of the demonstrated morbidity clusters. So far, studies investigating multimorbidity have focused largely on morbidity clusters of specific patient

Table 1. (Continued)

Surgery and orthopedics (n = 77,286 cases)	Gynecology and obstetrics (n = 21,979 cases)	Other (n = 7,245 cases)
53,955	17,717	4,526
1.43	1.24	1.60
63 (47–76)	34 (30–39)	64 (53–73)
34,422 (44.5)	21,968 (99.95)	3,566 (49.2)
4 (3–7)	5 (3–7)	3 (2–5)
69,616 (90.1)	21,203 (96.4)	6,263 (86.4)
6,483	2,448	1,188
1. Essential hypertension without hypertensive crisis (15.8)	1. Birth of a living singleton (58.5)	1. Secondary malignant neoplasm of the liver and intrahepatic bile ducts (31.2)
2. Accident, not further specified (15.3)	2. Pregnancy (49.1)	2. Irradiation in the personal anamnesis (25.8)
3. Essential hypertension without hypertensive crisis (12.1)	3. Secondary contractions (20.0)	3. Secondary malignant neoplasm of bone and bone marrow (14.4)
4. Medical incidents, not further specified (11.6)	4. Anemia complicating pregnancy, birth, and puerperium (16.4)	4. Primary wide angle glaucoma (13.0)
5. Diabetes mellitus type 2, without complications (9.2)	5. Complications of labor and delivery because of abnormal fetal heart rate (11.6)	5. Essential hypertension without hypertensive crisis (11.5)
5 (2–10)	4 (3–5)	2 (2–3)
1,180 (1.5)	38 (0.2)	1 (0.0)

populations with various techniques and disregarded unrelated diagnoses, which may not be clustered adequately [4]. As the co-occurrence frequency or mutual information of medical diagnoses may not per se be a marker of clinical importance in the management of multimorbidity, a high entropy in medical diagnoses could imply that management of multimorbid patients may be only partly streamlined by identification of common morbidity clusters. For instance, a rare genetic disease may drastically change the management of a multimorbid patient who otherwise only has diseases belonging to the cardiovascular and metabolic disease cluster [10–17]. Furthermore, multimorbidity patterns and clusters have been shown to often be heterogeneous across studies and to overlap with other disease clusters [4,6,16]. This may further complicate the comprehensive characterization of multimorbidity patterns and subsequent development of generalizable treatment strategies and guidelines for multimorbid patients.

As expected, we observed that the average number of diagnoses is rising with increasing age. Interestingly, the number of diagnosis pairs with mutual information scores >0.01 was higher in older inpatients, which may be

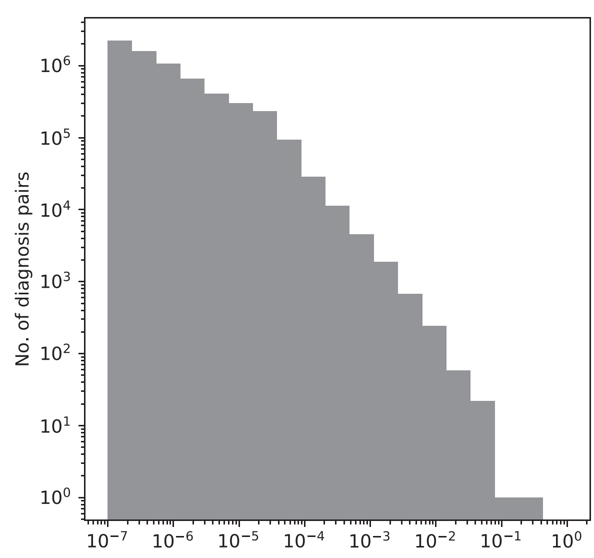

Fig. 2. Distribution of mutual information scores between diagnosis pairs (n = 190,837 inpatient cases).

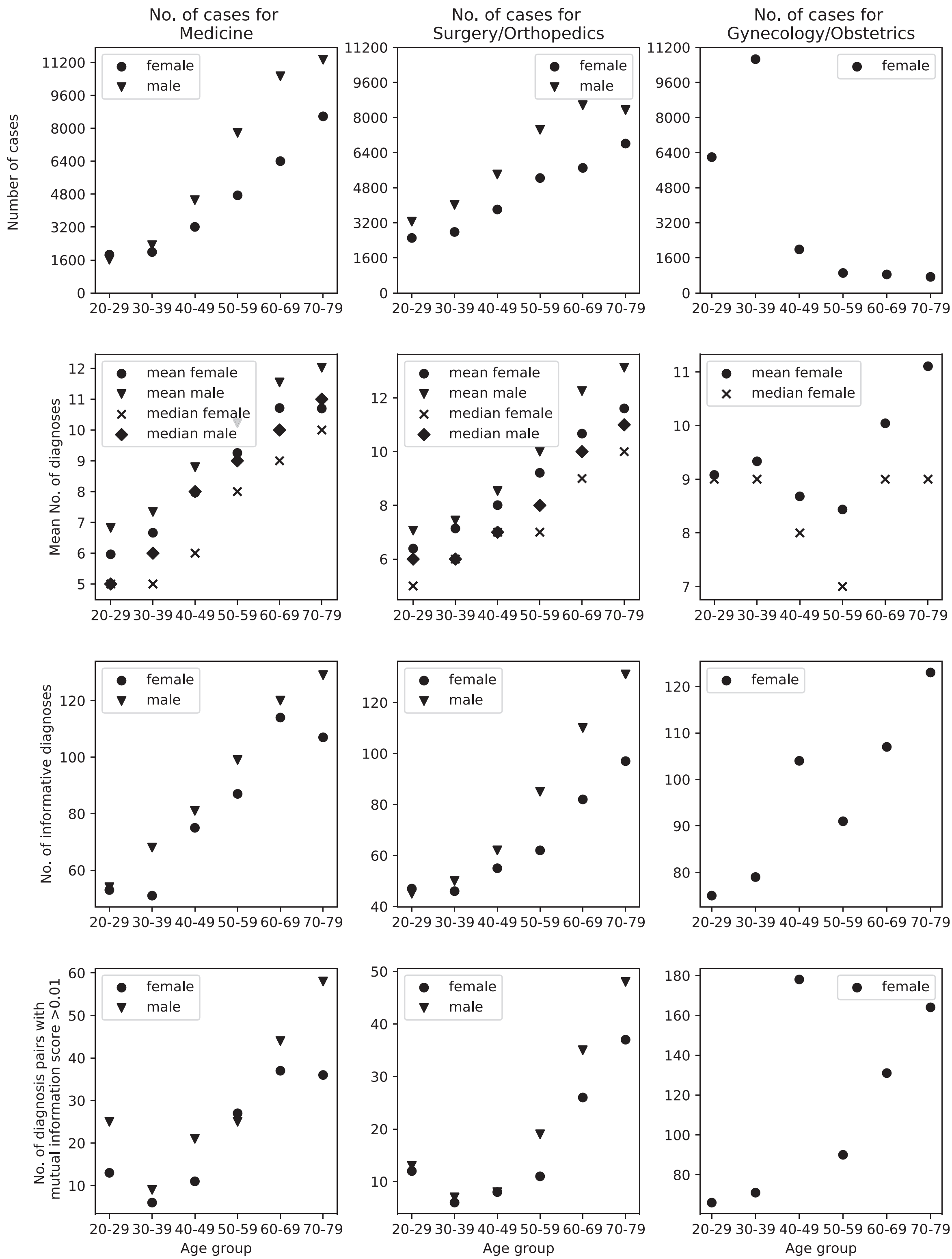

Fig. 3. Number of cases, mean number of diagnoses, number of informative diagnoses, and number of diagnosis pairs with mutual information scores >0.01 across age categories (n = 190,837 inpatient cases).

explained by the increased number of diagnoses in older inpatients: Having more diagnoses may also increase the likelihood of co-occurring diagnosis pairs. Still, the number of diagnosis pairs with high mutual information scores was relatively low across the highest age categories. This finding is particularly striking as some ICD-10 codes—even in a noncollapsed state—are relatively broad and may therefore share information with various other diagnostic codes. Furthermore, some of the diagnosis pairs with high mutual information scores merely reflect coding practices, complications of other diseases, and/or are part of the same disease complex (e.g., Alzheimer's disease—dementia due to Alzheimer's disease). We were surprised by the fact that the distribution of mutual information scores between diagnosis pairs was not bimodal (Fig. 2). We had expected that a substantial part of diagnosis pairs share almost no information (mode 1) and that some diagnosis pairs have high mutual information scores (mode 2). To our knowledge, the distribution of mutual information between medical diagnoses has not been studied so far. Such information distributions may help in guiding future studies that use mutual information analysis to mine large clinical or administrative databases. In our study, most diagnosis pairs with high mutual information scores (>0.01) were clinically well established. Novel, potentially causal relationships may often have lower mutual information scores, which could complicate the identification of promising diagnostic pairs for subsequent causal modeling, as small decreases in mutual information scores were frequently related to large increases in the number of diagnosis pairs (Fig. 2). Moreover, our data suggest that mutual information clustering may be used as a quality tool to explore factors that are associated with specific medical complications (Fig. 1). For instance, cluster number 7 may be considered as a complication cluster, as it comprises several postoperative complications such as hemorrhage and hematoma, acute bleeding anemia, delir, and infections. At the mutual information threshold of 0.01, these complications were not linked to a specific surgical site. In a follow-up study, associations with the respective complication cluster could be investigated further to identify potential risk factors, which are amenable to targeted interventions.

Our study is explorative in nature and has several limitations. First, we relied on ICD-10 codes, which may have led to misclassification of diagnoses during the coding process. We did not have internal validation data on the inter-rater agreement for coding ICD-10 diagnoses (e.g., kappa coefficient); however, all ICD-10 diagnoses were coded and checked by professional medical coders using standard criteria based on a complete and verified list of medical diagnoses—making it highly unlikely that diagnoses have been misclassified or fabricated. Second, we did not intend to draw causal inferences from disease patterns by applying certain hypothesis tests with specific type I error thresholds and by accounting for confounding effects; this was not deemed appropriate because of the cross-sectional study design and the high-dimensional and explorative nature of our study. Nonetheless, we stratified by sex and discipline to control for confounding effects between age categories and the average number of diagnoses as well as the number of informative diagnoses and diagnosis pairs with mutual information scores >0.01. Third, our study results may not be generalizable to other health care settings (e.g., ambulatory sector) and institutions that have different patient populations or that use other coding classifications. Restricting our analysis to specific patient populations and specific disease categories could have led to higher clustering effects and consequently higher mutual information scores between diagnoses. Fourth, we did not collapse ICD-10 codes before analysis; this could have resulted in higher mutual information scores between some broad diagnostic categories. We chose a priori not to analyze collapsed ICD-10 codes, as these categories are often too broad to be amenable to direct clinical interventions. Fifth, we included ICD-10 codes of the R and Z chapters in the analysis, which often describe symptoms, signs, and conditions that are not described elsewhere but that may be the consequence of active diseases; this may slightly change the mutual information distribution. Finally, we used a pragmatic approach and performed our analyses on a case level and not on a longitudinal patient level. Modeling temporal relationships have been shown to be helpful in interpreting clinical disease combinations (e.g., reverse causality) and to identify potential complications of diseases [18].

5. Conclusions

As part of an explorative analysis, we observed a high entropy, that is, unrelatedness, of diagnoses in a tertiary-care inpatient population. This finding indicates that although multimorbidity patterns can be observed, inpatient cases frequently have further diagnoses, which are unrelated to specific other diagnoses. Therefore, management of multimorbid patients should be individualized and may not be generalized based on a few multimorbidity patterns or clusters—especially in the light of precision medicine with increasing granularity of medical diagnoses. Mutual information may be a promising concept to characterize multimorbidity among different health care populations. Further studies are warranted to investigate specific causal relationships in multimorbidity patterns derived from mutual information analysis.

Acknowledgments

We thank Fabrice Juchler, MD, and Brian Duggan, both from the University Hospital Basel, Basel, Switzerland, for their help with the article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.01.003.

References

[1] Barnes PJ. Mechanisms of development of multimorbidity in the elderly. Eur Respir J 2015;45:790−806.

[2] Navickas R, Petric VK, Feigl AB, Seychell M. Multimorbidity: what do we know? What should we do? J Comorb 2016;6:4−11.

[3] van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol 1998;51:367−75.
[4] Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol 2014;67:254−66.
[5] Palmer K, Marengoni A, Forjaz MJ, Jureviciene E, Laatikainen T, Mammarella F, et al. Multimorbidity care model: recommendations from the consensus meeting of the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). Health Policy 2018;122:4−11.
[6] Nicholson K, Terry AL, Fortin M, Williamson T, Bauer M, Thind A. Examining the prevalence and patterns of multimorbidity in Canadian primary healthcare: a methodologic protocol using a national electronic medical record database. J Comorb 2015;5:150−61.
[7] Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015;12:e1001885.
[8] Roth JA, Goebel N, Sakoparnig T, Neubauer S, Kuenzel-Pawlik E, Gerber M, et al. Secondary use of routine data in hospitals: description of a scalable analytical platform based on a business intelligence system. JAMA Open 2018;1:172−7.
[9] Tourassi GD, Frederick ED, Markey MK, Floyd CE Jr. Application of the mutual information criterion for feature selection in computer-aided diagnosis. Med Phys 2001;28:2394−402.
[10] Garcia-Olmos L, Salvador CH, Alberquilla A, Lora D, Carmona M, Garcia-Sagredo P, et al. Comorbidity patterns in patients with chronic diseases in general practice. PLoS One 2012;7:e32141.
[11] Holden L, Scuffham PA, Hilton MF, Muspratt A, Ng SK, Whiteford HA. Patterns of multimorbidity in working Australians. Popul Health Metr 2011;9:15.
[12] John R, Kerby DS, Hennessy CH. Patterns and impact of comorbidity and multimorbidity among community-resident American Indian elders. Gerontologist 2003;43:649−60.
[13] Kirchberger I, Meisinger C, Heier M, Zimmermann AK, Thorand B, Autenrieth CS, et al. Patterns of multimorbidity in the aged population. Results from the KORA-Age study. PLoS One 2012;7:e30556.
[14] Newcomer SR, Steiner JF, Bayliss EA. Identifying subgroups of complex patients with cluster analysis. Am J Manag Care 2011;17:e324−32.
[15] Prados-Torres A, Poblador-Plou B, Calderon-Larranaga A, Gimeno-Feliu LA, Gonzalez-Rubio F, Poncel-Falco A, et al. Multimorbidity patterns in primary care: interactions among chronic diseases using factor analysis. PLoS One 2012;7:e32190.
[16] Schafer I, von Leitner EC, Schon G, Koller D, Hansen H, Kolonko T, et al. Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions. PLoS One 2010;5:e15941.
[17] Freund T, Kunz CU, Ose D, Szecsenyi J, Peters-Klimm F. Patterns of multimorbidity in primary care patients at high risk of future hospitalization. Popul Health Manag 2012;15:119−24.
[18] Hanauer DA, Ramakrishnan N. Modeling temporal relationships in large scale clinical associations. J Am Med Inform Assoc 2013;20:332−41.