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Article

A Bayesian Study of the Dynamic Effect of Comorbidities on Hospital Outcomes of Care for CHF Patients

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Abstract: Comorbidities can have a cumulative effect on hospital outcomes of care, such as the length of stay (LOS), and hospital mortality. This study examines patients hospitalized with Congestive Heart Failure (CHF), a life-threatening condition, which, when it coexists with a burdened disease profile, the risk for negative hospital outcomes increases. Since coexisting conditions co-interact, with a variable effect on outcomes, clinicians should be able to recognize these joint effects. In order to study CHF comorbidities, we used medical claims data from CMS. After extracting the most frequent cluster of CHF comorbidities, we: (i) Calculated, step-by-step, the conditional probabilities for each disease combination inside this cluster (ii) Estimated the cumulative effect of each comorbidity combination on the LOS and hospital mortality (iii) Constructed (a) Bayesian, scenario-based graphs and (b) Bayes-networks to visualize results. Results show that, for CHF patients, different comorbidity constructs have variable effect on the LOS and hospital mortality. Therefore, dynamic comorbidity risk assessment methods should be implemented for informed clinical decision making in any ongoing effort for quality of care improvements.

Keywords: comorbidities; congestive heart failure; health informatics; Bayes networks, clustering, risk assessment, clinical decision making

1. Introduction

In the recent years there is a high surge in the prevalence of chronic diseases with almost half adults having two or more chronic diseases [1]. Chronic diseases not only necessitate medical care and extensive use of healthcare resources, but also limit daily life activities and patient independence [2]. When a patient has a condition, chronic or not, in addition to his/her primary diagnosis (D_x), this disease is known as a comorbidity. Comorbidity is the presence of "a distinct additional clinical entity" [3] and is not related to the index condition or a side effect or result of treatment [4]. Comorbidities may or may not be directly related to the primary diagnosis [5]. For instance, a patient with a primary diagnosis of CHF may have hypertension (related condition) and chronic psoriasis (unrelated condition). Comorbidities can lead to patient complications and may trigger the need for hospitalization, oftentimes with a high risk for increased LOS, hospital-acquired conditions, and hospital death [6-8]. Their existence is important to be taken into consideration by physicians, because of their impact on the diagnosis, treatment, prognosis, and outcome [3].

Around 10,000 people in the United States turn 65 every day, and therefore there an anticipated ongoing increase in the number of individuals with comorbidities [9]. Several studies confirmed that chronic conditions appear together in clusters, as seen in the case of cardiovascular diseases [10-12, 14], while some clusters of comorbidities have been shown to have synergistic effect [13]. By

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identifying the aforementioned clustered clinical homogenous patient subgroups, it can become possible to develop better targeted and personalized interventions [2]. Treating patients for their comorbidity composition, and not separately for each diagnosis in silo, may contribute to tackling health problems more effectively, with improved coordination of care and integration of practice [9], in line with a holistic and patient centered care approach. Clinical guidelines hardly address comorbidities, and this can result in adverse events [10]. This emphasizes the importance of having patient-focused management and an efficient user-defined comorbidity system to identify risk factors and outcomes.

Researchers have studied outcomes and the prognosis in patients with multiple chronic diseases. Age and at least two comorbidities were found to be strong predictors for the development of hospital-acquired conditions (HAC), which in turn impact LOS negatively [15]. Nobili et al. found the presence of comorbidity increases mortality risk and LOS [16]. In addition, according to Parappil [17], patients with chronic obstructive pulmonary disease and comorbid diabetes have an increased LOS and elevated risk of death. Prolonged LOS is associated with adverse outcomes among other factors [18]. Because of all the aforementioned patient safety implications, it is critical for clinical decision makers to take into consideration the synergistic effect of various comorbidity profiles.

Using large healthcare datasets to stratify chronic conditions can contribute to improving the quality of care [9]. Health analytics methods, for instance, can be applied to study associations between risk factors and chronic conditions [19]. A systematic understanding of interactions between comorbidities can become possible with the support of data-driven technologies. These technologies can contribute to understanding and then planning to reduce preventable adverse outcomes of care.

In this study we examine the effect of comorbidity constructs on the LOS and hospital mortality, among elderly patients admitted to the hospital with a primary diagnosis of CHF, in the United States. Annually, over a million admissions occur in the United States for CHF [20] with more than 6.5 million hospital days and an economic burden of $37.2 billion [21]. Elderly with CHF have five or more comorbidities accounting for 40% of Medicare patients with high post-discharge mortality and readmission rates [20-23]. When a primary D_x of CHF is accompanied by comorbidities, the patient management and CHF treatment can become complicated: More than 30% of patients with CHF have comorbidities that worsen during hospitalization. These patients present increased mortality risk [21, 24] and prolonged hospital LOS, among other adverse hospital outcomes of care. For CHF patients, renal failure, COPD, diabetes, depression [22], hypertension, myocardial infarction, coronary artery disease, atrial fibrillation, anemia, chronic liver disease, and sleep-disordered breathing [25-27] were found to be predictors of LOS and hospital mortality.

While studies such as the aforementioned examine CHF comorbidities and their effect on hospital outcomes, they were not designed to compare outcomes of care between different comorbidity combinations. Also, existing studies do not examine the effect of a comorbidity on outcomes, when it is added onto a pre-existing disease construct. The objective of this work is to study the cumulative effect of comorbidities on the LOS and hospital mortality, for patients who have been diagnosed with CHF. Firstly, we used partitional clustering to find the most frequent hospital comorbidity construct (cluster) for patients with a primary diagnosis of CHF. We then extracted this cluster and calculated cumulative conditional probabilities for all comorbidity combinations within this cluster. These calculations served as the foundation for a visualized collection of directed acyclic graphs and Bayes Networks that can be navigated to examine the cumulative effect of any CHF comorbidity combination, on the two outcomes under study.

2. Materials and Methods

The research was conducted with a large medical claims dataset that was purchased from the Centers for Medicare and Medicaid Services (CMS). This dataset includes a 5% sample of Medicare hospital admissions that took place during the year 2014, includes 500,000 records and contains information about the patient admission, patient demographics, the ICD-9-CM diagnoses (Primary and Secondary), hospital-acquired conditions, hospital procedures, hospital charges and utilization variables. Medicare datasets have been used in a variety of studies to determine patient needs,

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suggest required services, and understand factors associated with negative outcomes. A variety of similar large healthcare datasets have also been used to study the effect of clinical practice on health outcomes [28], compare hospitals and their patient safety performance, and allow the in-depth study of rare conditions [29].

Since this study examines comorbidities of patients hospitalized with a primary diagnosis of CHF, we firstly filtered the data keeping only cases with a Primary diagnosis of CHF (ICD-9-CM: 428.0). This is the target dataset that was used for the analysis and contains 26,000 records (Fig. 1, Data Selection Phase).

The ICD codes (CHF comorbidities) were then grouped into Clinical Classification Software (CCS) codes. CCS is a grouping developed by the Agency of Healthcare Research and Quality (AHRQ) [30] to provide a meaningful clinical representation of diagnosis codes. CCS groups the thousands of unique ICD codes into 285 exclusive clinical categories. To transform diagnosis attributes from the ICD to the CCS coding system, a crosswalk, available at the AHRQ website was used. With the diagnosis attribute transformation to CCS, the data dimensionality was significantly reduced (285 dummy variables, one for each CCS code, instead of thousands of dummy ICD-9-CM variables) and the risk data overfitting was significantly minimized, with one small trade-off being small loss in diagnosis specificity (Fig. 1, Data Preparation Phase).

The data analysis includes two tasks (Fig. 1, Analytical Phase). Firstly, a coefficient analysis was completed using appropriate regression methods. The LOS, being a continuous variable was examined using Multiple Linear Regression. The study of hospital mortality, which is a dichotomous response was completed with Binary Logistic Regression. Regression coefficients were extracted from both models to find the CHF comorbidities associated with prolonged hospital day and high rates of mortality. The second task is the step-by-step calculation of the cumulative effect of CHF comorbidities on the LOS and hospital mortality. We decided to study contextually relevant CHF comorbidities and not just any random combination of comorbidities. For this reason, we extracted the most frequent CHF comorbidity set, by employing partitional clustering; for this frequent cluster of CHF comorbidities, we estimated, in a modular manner, for every combination of comorbidities, the mean LOS and hospital mortality, step by step, and visualized the constructs using directed acyclic graphs and Bayes Networks. Figure 1 shows an overview of the study methodology.

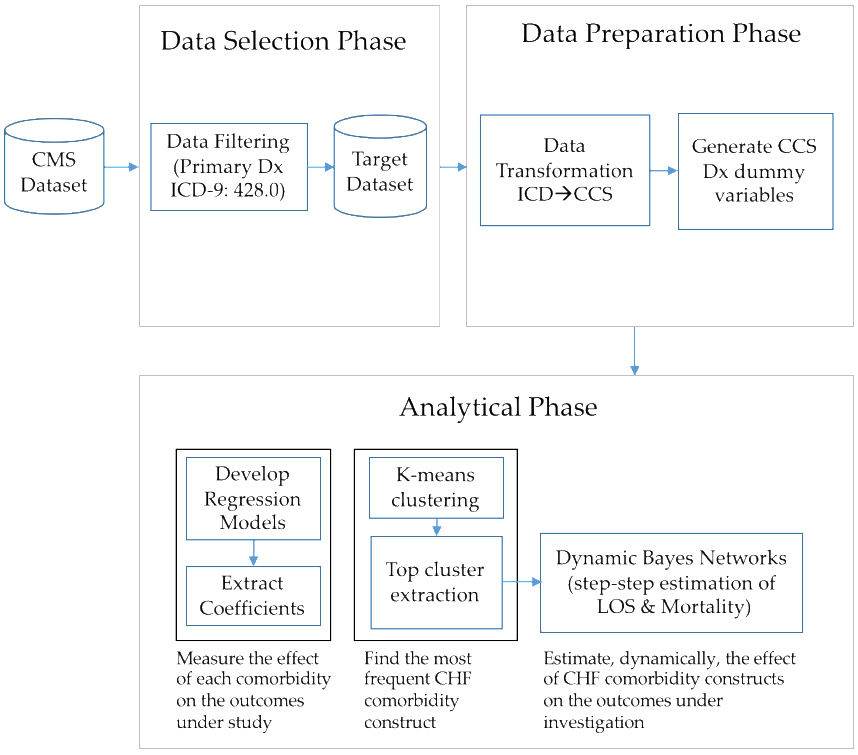

Figure 1. Overview of the study methodology

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3. Results

3.1. Descriptive Analysis: CHF Comorbidities with the longest LOS and highest hospital mortality

The average LOS and the mortality rate were calculated for every CHF comorbidity, to find the ones with the highest LOS and hospital mortality rate. As shown on Table 1, CHF patients and a secondary diagnosis of 'gangrene' (CCS=248), stay at the hospital, on average, 15.70 days. The second, in order, diagnosis associated with a prolonged stay was found to be 'shock' (LOS=14.76 days), followed by 'intestinal obstruction' (LOS=13.21 days). Regarding hospital mortality, for CHF patients with a comorbidity of 'cardiac arrest', the mortality rate is 51.7%, followed by 'shock' (mortality rate=32.9%) and 'septicemia' (mortality rate=21.9%). Table 1 shows the top ten CHF comorbidities with the longest LOS and the highest rates of hospital death.

Table 1. Comorbidities (N > 10) with the longest LOS and the highest mortality rate

CHF Comorbidity	**LOS (days)**	**N**
Gangrene (CCS=248)	15.70	64
Shock (CCS=249)	14.76	450
Intestinal obstruction w/o hernia (CCS=145)	13.21	127
Septicemia (CCS=2)	13.00	456
Acute post-hemorrhagic anemia (CCS=60)	12.58	356
Aspiration pneumonitis (CCS=129)	12.15	300
Acute cerebrovascular disease (CCS=109)	11.20	135
Cardiac arrest & ventricular fibrillation (CCS=107)	10.84	238
MHSA: Adjustment disorders (CCS=650)	10.77	53
Complication of surgical /medical procedure (CCS=238)	10.49	533
CHF Comorbidity	**Mortality (%)**	**N**
Cardiac arrest & ventricular fibrillation (CCS=107)	51.7	238
Shock (CCS=249)	32.9	450
Peritonitis and intestinal abscess (CCS=148)	26.9	26
Septicemia (CCS=2)	21.9	456
Aspiration pneumonitis (CCS=129)	19.3	300
Prolapse of female genital organs (CCS=170)	18.2	11
Intestinal obstruction w/o hernia (CCS=145)	18.1	127
Liver Ca and intrahepatic bile duct (CCS=16)	17.2	29
Cancer of the esophagus (CCS=12)	15.8	38
Gangrene (CCS=248)	15.6	64

3.2. Analytical Phase-Task 1: Coefficient Analysis

3.2.1. Length of Stay

To estimate the effect of each individual CHF comorbidity on the hospital LOS, a multiple linear regression model was created, with LOS being the dependent variable. All the CHF comorbidities (dummy CCS variables) were inserted to the model as independent variables. The regression model was found to explain the 30.7% of LOS variability (R^2=0.307). The regression coefficients provided information about the strength of association between each CHF comorbidity and the LOS. The CHF comorbidity 'gangrene' (CCS=248) was found to have the strongest effect on the LOS (b=6.89, p<0.001): When a CHF patient develops 'gangrene' the LOS increases by almost 7 days. Similarly, when a CHF patient develops 'shock', the LOS increases by almost 5 days (b=4.96, p<0.001). The presence of the CHF comorbidity 'adjustment disorders' increases the LOS by almost 5 days (b=4.73, p<0.001), while a CHF patient with 'intestinal obstruction without hernia' will have a LOS increase of more than 4 days (b= 4.32, p<0.001). Table 2 presents the top ten CHF comorbidities with the strongest association with the LOS.

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Table 2. Coefficient analysis of the LOS using multiple linear regression

CHF Comorbidity	b	S.E.	p-value
Gangrene (CCS=248)	6.89	0.55	<0.001
Shock (CCS=249)	4.96	0.21	<0.001
Adjustment disorders (CCS=650)	4.73	0.59	<0.001
Intestinal obstruction w/o hernia (CCS=145)	4.32	0.38	<0.001
Aspiration pneumonitis (CCS=129)	3.63	0.25	<0.001
Acute cerebrovascular disease (CCS=109)	3.53	0.38	<0.001
Acute hemorrhage anemia (CCS=60)	3.46	0.24	<0.001
Diseases of the mouth (CCS=137)	2.89	0.61	<0.001
Complications (surg./med) (CCS=238)	2.89	0.19	<0.001
Septicemia (CCS=2)	2.71	0.21	<0.001

3.2.2. Hospital Mortality Rate

To estimate the odds ratio of each individual CHF comorbidity for hospital death (dichotomous outcome), a Multiple Binary Logistic regression model was created. All the CHF comorbidities (dummy CCS variables) were inserted to the model as independent variables. The hospital death indicator was the dependent variable of the model. This regression analysis was employed to estimate the effect of the CHF comorbidities on the mortality rate, for hospitalized CHF patients. According to findings, 'cardiac arrest & ventricular fibrillation' (CCS=107) has the strongest association with the mortality rate (OR=30.50, p<0.001) with odds for hospital death increasing by 30 times. The CHF comorbidity 'peritonitis & intestinal abscess' (OR=14.42, p<0.001) and 'genital organ prolapse' (OR=12.92, p<0.01) increase the odds for hospital death by 14 and by 13 times respectively. Table 3 shows the top ten comorbidities with the strongest association with the hospital mortality.

Table 3. Coefficient analysis of mortality rate using binary logistic regression:

CHF Comorbidity	O.R.	S.E.	p-value
Cardiac arrest & ventric. fibril. (CCS=107)	30.50	0.17	<0.001
Peritonitis & intestinal abscess (CCS=148)	14.42	0.63	<0.001
Prolapse female gen. organs (CCS=170)	12.92	0.87	0.004
Cancer of the esophagus (CCS=12)	10.03	0.54	<0.001
Cancer of the liver (CCS=16)	8.07	0.63	0.001
Shock (CCS=249)	6.72	0.15	<0.001
Gangrene (CCS=248)	4.04	0.50	0.006
Acute cerebrovascular disease (CCS=109)	3.55	0.32	<0.001
Intestinal obstruction w/o hernia (CCS=145)	3.15	0.32	<0.001
Respiratory failure; arrest (CCS=131)	2.76	0.08	<0.001

3.3. Analytical Phase-Task 2: Dynamic navigation of CHF comorbidity scenarios and their effect on outcomes

We started by extracting the most frequent CHF comorbidity cluster for a contextually relevant study of the cumulative effect of CHF comorbidities on the LOS and the hospital mortality. To do this, we used the Weka (https://www.cs.waikato.ac.nz/ml/weka/) implementation of k-means, a partitional clustering algorithm. By plotting the within-cluster sum of square errors of the test set for different k's (number of cluster scenarios) we observed an error stability (line graph forms an 'elbow') when k=7. According to the elbow criterion we proceeded with the parameter k=7 and generated seven clusters, of which we extracted the most frequent one, for further study. Table 4 shows the output of the simple k-means experiment. Each cluster represents comorbidities that frequently coexist. The cluster that groups most of the instances and that we extracted for further study is Cluster 1. This cluster groups together the CHF comorbidities: *'disorders of lipid metabolism'*, *'deficiency and other anemia'*, *'hypertension with complications/secondary hypertension'*, *'coronary atherosclerosis and other heart disease'*, and *'chronic kidney disease'*.

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Table 4. Clustering of CHF comorbidities using the k-means partitional algorithm

CHF Comorbidities	Clustered instances
Cluster 1: 'disorders of lipid metabolism' (CCS=53), 'deficiency and other anemia' (CCS=59), 'hypertension with complications and secondary hypertension' (CCS=99), 'coronary atherosclerosis and other heart disease' (CCS=101), 'chronic kidney disease' (CCS=158)	7565 (29%)
Cluster 2: 'fluid & electrolyte disorders' (CCS=55), 'nutritional endocrine; and metabolic disorders' (CCS=58), 'chronic obstructive pulmonary disease and bronchiectasis' (CCS=127), 'respiratory failure' (CCS=131)	2181 (9%)
Cluster 3 'essential hypertension' (CCS=98)	4562 (18%)
Cluster 4 'essential hypertension' (CCS=98), 'disorders of lipid metabolism' (CCS=53), 'coronary atherosclerosis and other heart disease' (CCS=101), 'cardiac dysrhythmias' (CCS=106)	5759 (22%)
Cluster 5 'cardiac dysrhythmias' (CCS=106), 'fluid & electrolyte disorders' (CCS=55), 'deficiency & other anemia' (CCS=59), 'hypertension with complications/secondary hypertension' (CCS=99), 'chronic kidney disease' (CCS=158), 'heart valve disorders' (CCS=96), 'pulmonary heart disease' (CCS=103)	2098 (8%)
Cluster 6 'deficiency and other anemia' (CCS=59), 'hypertension with complications and secondary hypertension' (CCS=99), 'chronic kidney disease' (CCS=158), 'coronary atherosclerosis and other heart disease' (CCS=101), 'chronic obstructive pulmonary disease and bronchiectasis' (CCS=127), 'respiratory failure; insufficiency; arrest (adult)' (CCS=131), 'diabetes mellitus without complications' (CCS=49), 'acute and unspecified renal failure' (CCS=157)	2284 (9%)
Cluster 7 'respiratory failure; arrest' (CCS=131), 'cardiac dysrhythmias' (CCS=106), 'fluid & electrolyte disorders' (CCS=55), 'essential hypertension' (CCS=98), 'screening & history of mental health & substance abuse' (CCS=663)	1198 (5%)

The next step involves the estimation of the mean LOS and mortality rate for every different combination inside Cluster 1 (CCS=53, CCS=59, CCS=99, CCS=101, CCS=158). For every combination, new dummy variables were stored into the database to facilitate creation of conditional probability tables on demand (Table 5). For instance, for the combination 'lipid metabolism disorders' (CCS=53) and 'deficiency and other anemia' (CCS=59), a new variable will be generated, based on the condition:

IF CCS(53)=1 AND CCS(59)=1 AND CCS(99)=0 AND CCS(101)=0 AND CCS(158)=0
THEN [CCS(53) Λ CCS(59)] = 1
ELSE [CCS(53) Λ CCS(59)] = 0

This condition triggers the addition, to the dataset, of a new variable, with values of '1' for instances where {CCS53=1, CCS59=1, CCS99=0, CCS101=0, CCS158=0}. We then calculated, the mean LOS, the mortality rate, and the 95% C.I of the means, for the '1' cases, for all possible combinations of the Cluster 1 contents (total=2^5 =32 combinations) and constructed conditional probability tables, that show the cumulative effect of any comorbidity construct. The conditional probability tables were also visualized with step-by step Bayesian graphs of comorbidity constructs, to better understand the additive effect of CHF comorbidities on the two outcomes under study.

Table 5. Mortality rate and mean LOS for every CHF Comorbidity combiniation within Cluster 1

Combinations of CHF Comorbidities	N	Mortality rate (%) (95% C.I)	Mean LOS (days) (95% C.I)
53	1598	2.37 (1.63-3.12)	4.26 (4.10-4.43)
53+59	508	1.57 (0.49-2.65)	5.17 (4.83-5.51)
53+59+99	21	4.76 (0.00-14.09)	5.23 (3.61-6.86)
53+59+99+101	51	3.92 (0.00-9.30)	6.27 (4.53-8.01)
53+59+99+101+158	2148	2.61 (1.93-3.28)	5.82 (5.60-6.04)

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59	898	4.34 (0.68-3.01)	5.54 (5.25-5.82)
59+99	42	2.38 (0.00-7.04)	6.71 (4.94-8.48)
59+99+101	34	2.94 (0.00-8.79)	6.18 (4.26-8.01)
59+99+101+158	1294	2.71 (1.82-3.58)	6.11 (5.77-6.45)
53	1598	2.37 (1.63-3.12)	4.26 (4.10-4.43)
53+99	95	0.00 (0.00-0.00)	4.63 (3.76-5.49)
53+99+101	144	1.38 (0.00-3.31)	5.50 (4.41-6.59)
53+99+101+158	2308	3.25 (2.52-3.97)	4.93 (4.74-5.12)

3.3.1. Directed acyclic graphs for comorbidity construct scenarios

After having estimated the LOS and mortality rate for the different combination constructs of the cluster {*metabolism disorders, anemia, hypertension with complications, coronary atherosclerosis, chronic kidney disease*}, results were visualized with directed acyclic graphs. The graphs show the apparent change to the two outcomes of interest for different scenarios of comorbidity constructs. Each new graph node represents an addition of a new diagnosis on top of the preceding one. The user can follow any of the fifteen different paths, as shown in Fig. 2 and see the updated LOS and mortality rate. In the majority of the paths, the mortality rate and the LOS increases as more CHF comorbidities are added. Characteristically, for CHF patients who only have 'disorders of lipid metabolism' (CCS=53), the mean LOS is 4.26 days (95% C.I = 4.10-4.43). When 'deficiency and other anemia' (CCS=59) is added to the profile, the mean LOS increases to 5.17 days (95% C.I =4.83-5.51). When on top of these two comorbidities, the patient is diagnosed with 'hypertension with complications' (CCS=99), the mean LOS further increases to 5.23 days (95% C.I = 3.61-6.86). Finally, new LOS increase is observed with the addition of 'coronary atherosclerosis' (CCS=101), up to 6.27 days (95% C.I = 4.53-8.01). In the same manner, while the exclusive presence of 'coronary atherosclerosis and other heart disease' (CCS=101) is associated with a mean mortality rate of 2.75%, when 'chronic kidney disease' (CCS=158) is added to this patient scenario, the mortality rate increases up to 6.19%.

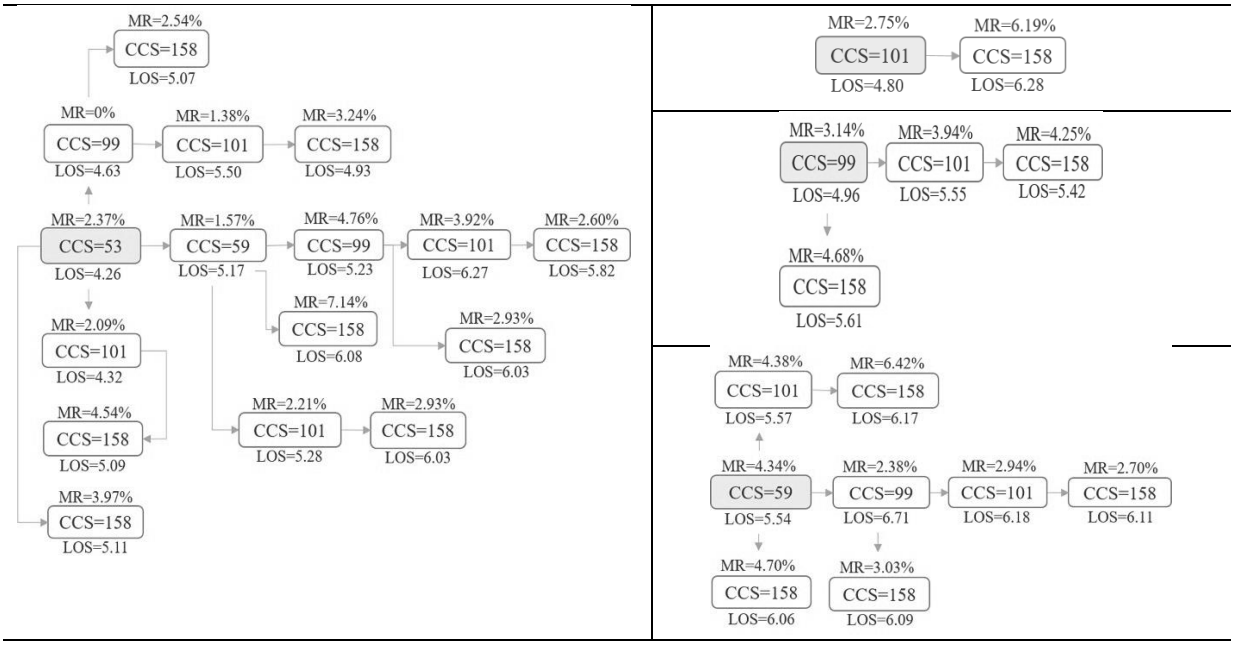

Figure 2. Effects of comorbidity constructs on LOS and mortality rate

Interestingly, some comorbidities may have a different effect on outcomes, depending on the preexisting disease set that the new diagnosis has been added onto. For instance, although the mean LOS and the mortality rate both remain the same when 'coronary atherosclerosis' (CCS=101) is added on top of 'disorders of lipid metabolism' (CCS=53), this is not the case when CCS=101 is added on top of CCS=99 (hypertension with complications). Evidently, for patients with CHF, the 'coronary

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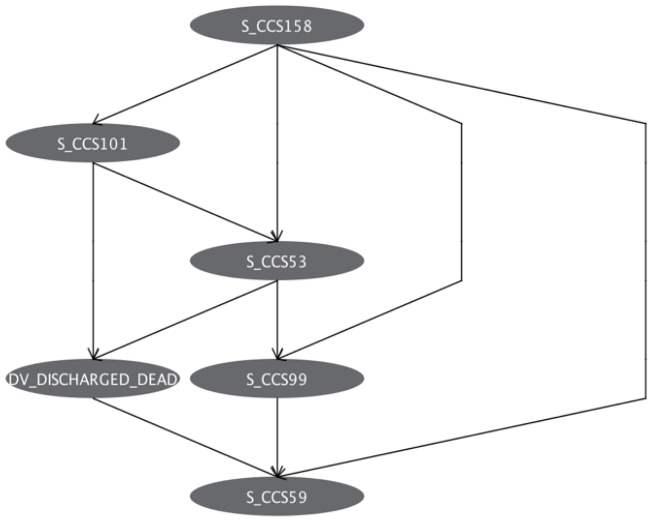
atherosclerosis' and 'hypertension with complications' combination is a more severe 'diagnosis blend' than that of 'coronary atherosclerosis' with 'disorders of lipid metabolism'.

3.3.2. Bayesian Networks of CHF comorbidities

The second goal of task 2 was to construct Bayes Networks for CHF comorbidities included in Cluster 1, for the dichotomous outcome 'hospital death'. While we previously visualized all combinations of comorbidity constructs, we now present a supervised representation of associations between comorbidities and the 'hospital death', based on a trained Bayes Net model. Using Weka, we developed a Bayes Network using the Simple Estimator, which estimates the conditional probability tables of a Bayes network once the structure has been learned. We used a Genetic Search algorithm with Markov blanket correction. The Markov blanket correction was applied to the network structure, to enhance the information included in the values of the parents and children of the network nodes.

The top patent node of the trained Bayes Network is CCS=158 (chronic kidney disease). Its four child notes are the four remaining comorbidities of Cluster 1 (most frequent CHF comorbidity group). The outcome under investigation (hospital death) has two direct parent nodes: CCS=53 (lipid metabolism disorders) and CCS=101 (coronary atherosclerosis and other heart disease). Fig. 3 shows the network, as it was visualized by the Weka Classifier Graph Visualizer (left) and the probability distribution table to the 'hospital death' node (right). While we hereby present the Bayes Network for Cluster 1, similar Bayes Network graphs can be generated, following the same approach, for any of the remaining CHF comorbidity clusters.



CCS=53	CCS=101	0	1
0	0	0.96	0.04
0	1	0.965	0.035
1	0	0.975	0.025
1	1	0.974	0.026

Figure 3: Left: Bayesian Network of CHF Comorbidities included in the most frequent cluster. **Right:** Probability distribution table for the dependent variable 'hospital death'

4. Discussion

This study examined the prevalence and cumulative effect of CHF comorbidities for elderly patients with a primary diagnosis of CHF, using medical claims data. The study presented an in-depth exploration of comorbidities for one of the most frequent reasons for hospitalization in the United States and also introduced Bayes-based methods to understand the cumulative burden of comorbidities on negative outcomes of hospital care.

A significant burden of comorbidity was observed in CHF patients with two or more comorbidities. The most common CHF comorbidities associated with an increased LOS were found to be 'gangrene', 'shock', 'intestinal obstruction without hernia', and 'adjustment disorders'. Another study that examined psychosocial factors and other comorbidities in CHF patients, also found that

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'adjustment disorders' are associated with as increasing LOS and mortality rate [22, 31]. Regression based coefficient analysis, showed that for an increase of 1 unit to value of the 'gangrene' variable (change from '0' to '1'), the LOS increases by 6.90 days ($p<0.001$). Similarly, other secondary D_x's that were found to be associated with and increased LOS were 'shock' (LOS=4.97, $p<0.001$) [33], 'adjustment disorders' (LOS=4.73, $p<0.001$), and 'intestinal obstruction without hernia' (LOS=4.33, $p<0.001$). 'Anemia' in patients with CHF was also found to be associated with prolonged hospital stay in a previous study [34], with findings similar to our current study.

As far as the mortality rate is concerned, we found that comorbidities associated with increased mortality rate are the 'cardiac arrest and ventricular fibrillation', 'acute cerebrovascular disease' [32], 'peritonitis and intestinal abscess', 'prolapse of female genital organs', 'shock', and 'cancer of the esophagus'. Results of multiple binary logistic regression reveal that the CHF comorbidity 'cardiac arrest and ventricular fibrillation' (CCS=107) is associated with a 30.5 increase to the odds for hospital death. Other CHF comorbidities that were found to increase mortality risk are 'peritonitis and intestinal abscess' (OR=14.4), 'prolapse of female genital organs' (OR=12.9), 'cancer of the esophagus' (OR=10.0), 'shock' (OR=6.721) [35], and 'acute cerebrovascular disease' (OR=3.559) [36]. In similar studies the 'acute myocardial infarction', and 'acute and unspecified renal failure' diagnoses were also found to be associated with a significant increase to the odds for hospital death, for patients with a primary diagnosis of CHF [37, 38].

Several studies have shown that comorbidities have a significant impact on survival and LOS in CHF patients, and our study results are in agreement. Our study shows that comorbidities can have a variable effect of these outcomes, according to the comorbidity construct they belong to. We therefore recognize the need for the development of comorbidity-specific software risk estimation add-ons to existing clinical decision support systems that quantify the different risk levels for those patients. This will facilitate data-driven, informed decision making and improved patient counseling. The need for such systems and mechanisms have been discussed and recommended in the literature [32] in an effort to assist physicians provide "individualized person-centered care" [31].

Our study and the "block-by-block" comorbidity construction approach is an effort to this direction. It is imperative for physicians to recognize common comorbidities for their patients and understand the effect of comorbidities on outcomes of care. As this work shows, for CHF patients, different comorbidity constructs may have variable effect on the outcomes. Identifying the prevalence and quantifying their cumulative effect for patients will provide evidence for informed clinical decision making in any ongoing effort for improvements to the quality of care. There is more research to be done in order to develop and provide comorbidity-specific recommender tools to clinical decision makers and quality improvement specialists. The authors finally believe that education and training of medical professionals and residents should utilize large healthcare datasets, and assist future professionals in recognizing common comorbidities, and their effect on critical outcomes of care.

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References

1. Centers for Disease Prevention and Control (2019). Chronic diseases in America. Accessed from https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm
2. U.S. Department of Health and Human Services. Multiple chronic conditions—a strategic framework: Optimum health and quality of life for individuals with multiple chronic conditions. Washington, DC. December 2010. http://www.hhs.gov/ash/initiatives/mcc/mcc_framework.pdf.
3. Feinstein, A. R. (1970). The pre-therapeutic classification of co-morbidity in chronic disease. *Journal of Chronic Diseases*, *23*(7), 455–468.
4. Piccirillo, J. F., & Costas, I. (2004). The Impact of Comorbidity on Outcomes. *ORL*, *66*(4), 180–185.
5. Jones, R. (2010). Chronic Disease and Comorbidity. *The British Journal of General Practice*, *60*(575), 394.
6. Comlossy M. (2013). Chronic Disease Prevention and Management. National Conference of State Legislatures; Denver, CO, USA: 2013. http://www.ncsl.org/documents/health/ChronicDTK13.pdf
7. Centers for Disease Control (2009). The Power of Prevention: Chronic Disease the Public Health Challenge of the 21st Century. Available online: www.cdc.gov/chronicdisease/pdf/2009-Power-of-Prevention.pdf
8. Gijsen, R., Hoeymans, N., Schellevis, F. G., Ruwaard, D., Satariano, W. A., & van den Bos, G. A. M. (2001). Causes and consequences of comorbidity: A review. *Journal of Clinical Epidemiology*, *54*(7), 661–674. https://doi.org/https://doi.org/10.1016/S0895-4356(00)00363-2
9. Tinker A. (2014). How to Improve Patient Outcomes for Chronic Diseases and Comorbidities. online: http://www.healthcatalyst.com/wp-content/uploads/2014/04/How-to-Improve-Patient-Outcomes.pdf
10. Buja, A., Claus, M., Perin, L., Rivera, M., Corti, M. C., Avossa, F. et al. (2018). Multimorbidity patterns in high-need, high-cost elderly patients. *PloS One*, *13*(12), e0208875–e0208875.
11. Goodman, R. A., Briss, P. A., Ling, S. M., Parrish, R. G., Salive, M. E., & Finke, B. S. (2015). Multimorbidity Patterns in the United States: Implications for Research and Clinical Practice. *The Journals of Gerontology: Series A*, *71*(2), 215–220.
12. Schäfer, I., von Leitner, E.-C., Schön, G., Koller, D., Hansen, H., Kolonko, T. et al. (2010). Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions. *PloS One*, *5Schäfer,* (12), e15941–e15941.
13. Wolff J.L, Starfield B, Anderson G. (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*;162 (20):2269–2276.
14. Islam, M.M., Valderas, J. M., Yen, L., Dawda, P., Jowsey, T., & McRae, I. S. (2014). Multimorbidity and comorbidity of chronic diseases among the senior Australians: prevalence and patterns. *PloS One*, *9*(1), e83783–e83783.
15. Wen, T., He, S., Attenello, F., Cen, S. Y., Kim-Tenser, M., Adamczyk, P. et al. (2014). The impact of patient age and comorbidities on the occurrence of "never events" in cerebrovascular surgery: an analysis of the Nationwide Inpatient Sample. *Journal of Neurosurgery JNS*, *121*(3), 580–586.
16. Nobili, A., Licata, G., Salerno, F., Pasina, L., Tettamanti, M., Franchi, C. et al. (2011). Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *European Journal of Clinical Pharmacology*, *67*(5), 507–519.
17. Parappil, A., Depczynski, B., Collett, P., & Marks, G. B. (2010). Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. *Respirology*, *15*(6), 918–922.
18. Wiler, J.L., Handel, D.A., Ginde, A.A., Aronsky, D., Genes, N. G., Hackman, J.L et al. (2012). Predictors of patient length of stay in 9 emergency departments. *The American Journal of Emergency Medicine*, *30*(9), 1860–64.
19. Barrett, M. A., Humblet, O., Hiatt, R. A., & Adler, N. E. (2013). Big Data and Disease Prevention: From Quantified Self to Quantified Communities. *Big Data*, *1*(3), 168–175.
20. Ambrosy, A. P., Fonarow, G. C., Butler, J., Chioncel, O., Greene, S. J., Vaduganathan, M. et al. (2014). The Global Health and Economic Burden of Hospitalizations for Heart Failure: Lessons Learned from Hospitalized Heart Failure Registries. *Journal of the American College of Cardiology*, *63*(12), 1123–1133.
21. Gheorghiade, M., Vaduganathan, M., Fonarow, G. C., & Bonow, R. O. (2013). Rehospitalization for Heart Failure: Problems and Perspectives. *Journal of the American College of Cardiology*, *61*(4), 391–403.
22. Braunstein, J. B., Anderson, G. F., Gerstenblith, G., Weller, W., Niefeld, M., Herbert, R., & Wu, A. W. (2003). Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. *Journal of the American College of Cardiology*, *42*(7), 1226–1233.

23. Marti, C. N., Fonarow, G. C., Gheorghiade, M., & Butler, J. (2013). Timing and duration of interventions in clinical trials for patients with hospitalized heart failure. *Circulation. Heart Failure*, *6*(5), 1095–1101.
24. Abraham, W. T., Adams, K. F., Fonarow, G. C., Costanzo, M. R., Berkowitz, R. L., LeJemtel, T. H., … Wynne, J. (2005). In-Hospital Mortality in Patients with Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications: An Analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *Journal of the American College of Cardiology*, *46*(1), 57–64.
25. Triposkiadis, F., Giamouzis, G., Parissis, J., Starling, R. C., Boudoulas, H., Skoularigis, J. et al. (2016) Reframing the association and significance of co-morbidities in heart failure. *European Journal of Heart Failure*, *18*(7), 744–758.
26. Szwejkowski, B. R., Elder, D. H. J., Shearer, F., Jack, D., Choy, A. M. J., Pringle, S. D. et al. (2012). Pulmonary hypertension predicts all-cause mortality in patients with heart failure: a retrospective cohort study. *European Journal of Heart Failure*, *14*(2), 162–167.
27. Scrutinio, D., Passantino, A., Guida, P., Ammirati, E., Oliva, F., Braga, S. S et al. (2016). Prognostic impact of comorbidities in hospitalized patients with acute exacerbation of chronic heart failure. *European Journal of Internal Medicine*, *34*, 63–67.
28. Kucharska-Newton AM, Heiss G, Ni H, Stearns SC, Puccinelli-Ortega N, Wruck LM, et al. Identification of Heart Failure Events in Medicare Claims: The Atherosclerosis Risk in Communities (ARIC) Study. J Card Fail. 2016; 22(1):48–55.
29. Menis M, Forshee RA, Kumar S, McKean S, Warnock R, Izurieta HS, et al. Babesiosis occurrence among the elderly in the United States, as recorded in large Medicare databases during 2006-2013. PLoS One. 2015;10 (10).
30. Healthcare Cost and Utilization Project. Clinical Classifications Software (CCS) for ICD-9-CM. Available from: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp
31. Lawson, C.A., Solis-Trapala, I., Dahlstrom, U., Mamas, M., Jaarsma, T., Kadam, U.T., & Stromberg, A. (2018). Comorbidity health pathways in heart failure patients: A sequences-of-regressions analysis using cross-sectional data from 10,575 patients in the Swedish Heart Failure Registry. *PLOS Medicine*, *15*(3), e1002540.
32. Kwok, C.S., Olier, I., Rashid, M., Mamas, M.A., Gale, C.P., Doherty, P. et al. (2016). Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. *European Heart Journal - Qual of Care and Clinical Outcomes*, *3*(1), 20–36.
33. Scott, E. C., Ho, H. C., Yu, M., Chapital, A. D., Koss, W., & Takanishi, D.M. (2008). Pre-Existing Cardiac Disease, Troponin I Elevation and Mortality in Patients with Severe Sepsis and Septic Shock. *Anaesthesia and Intensive Care*, *36*(1), 51–59.
34. Young, J.B., Abraham, W.T., Albert, N.M., Gattis Stough, W., Gheorghiade, M., Greenberg, B.H. et al. (2008). Relation of Low Hemoglobin and Anemia to Morbidity and Mortality in Patients Hospitalized with Heart Failure (Insight from the OPTIMIZE-HF Registry). *The American Journal of Cardiology*, *101*(2), 223–230.
35. Mebazaa, A., Tolppanen, H., Mueller, C., Lassus, J., DiSomma, S., Baksyte, G., Januzzi, J. (2016). Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance. *Intensive Care Medicine*, *42*(2), 147–63.
36. Lee, D.S., Austin, P.C., Rouleau, J.L., Liu, P.P., Naimark, D., & Tu, J.V. (2003). Predicting Mortality Among Patients Hospitalized for Heart Failure Derivation and Validation of a Clinical Model. *JAMA*, *290*(19), 2581-87.
37. Krumholz, H. M., Chen, Y.-T., Vaccarino, V., Wang, Y., Radford, M. J., Bradford, W. D., & Horwitz, R. I. (2000). Correlates and impact on outcomes of worsening renal function in patients ≥65 years of age with heart failure**.** *The American Journal of Cardiology*, *85*(9), 1110–1113.
38. Forman, D. E., Butler, J., Wang, Y., Abraham, W. T., O& Connor, C. M., Gottlieb, S. S. et al. (2004). Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *Journal of the American College of Cardiology*, *43*(1), 61 LP-67.